Physiological Assessment of the Load-Capacity-Drive Relationship in Chronic Respiratory Failure and Outcomes following Domiciliary Non-Invasive Ventilation

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Physiological Assessment of the Load-Capacity-Drive Relationship in Chronic Respiratory Failure and Outcomes following Domiciliary Non-Invasive Ventilation

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CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABSTRACT

Background: Acute and chronic respiratory failure occurs as a consequence of an imbalance in the load-capacity-drive relationship of the respiratory system. Despite the high morbidity and mortality of these patients, clear clinical strategies for assessment and subsequent management have been lacking due to the limited high quality data available. The aim of this thesis was to evaluate novel techniques to monitor patients with acute respiratory deterioration as well as the use of specific monitoring and non-invasive ventilation strategies in patients with chronic respiratory failure, which could translate into important clinical benefits.

Methods: Three clinical physiological studies were performed. Firstly, a randomised controlled trial evaluated an automated novel hybrid pressure-volume mode of non-invasive ventilation to treat obesity hypoventilation syndrome. Although the primary outcome measure was gas exchange at three months, important physiological measures including physical activity, sleep quality and their relationship to weight loss were also investigated. Secondly, an observational cohort trial investigated the role of a novel advanced physiological biomarker, neural respiratory drive, to identify treatment failure and readmission risk in patients admitted to hospital with an acute exacerbation of chronic obstructive pulmonary disease. The third physiological trial investigated, in patients with persistent hypercapnic respiratory failure following an acute exacerbation of COPD as part of a large randomised controlled trial, the efficacy and mechanism of action of home mechanical ventilation and its effect on sleep quality compared with standard oxygen therapy.

Results: The automated volume targeted mode of ventilation demonstrated no advantage in physiological and clinical outcomes above a nurse-led protocolised standard set up of non-invasive ventilation in the management of obesity hypoventilation syndrome. The trial was the first to demonstrate that the management of sleep disordered breathing and chronic respiratory failure in obesity hypoventilation syndrome confers an improvement in objectively assessed physical activity as well as weight loss, which has important clinical implications. In the second trial, neural respiratory drive was validated as a

novel physiological biomarker to monitor acute clinical change during hospital treated exacerbations of COPD. Furthermore, patients in whom neural respiratory drive failed to fall in response to treatment prior to hospital discharge had a significantly higher risk of hospital readmission within 14 days, again, highlighting the important clinical implications of detailed physiological observations. The third physiological trial confirmed previous data indicating that an important mechanism of action of home mechanical ventilation in COPD is through improvements in central respiratory drive, but this conclusion was given greater confidence by the use of advanced physiological monitoring.

Conclusion: The data presented in this thesis provide clinically important information on the physiological targeting of set-up of non-invasive ventilation in patients with chronic respiratory failure secondary to obesity hypoventilation syndrome and severe COPD. Important markers of treatment success in the management of chronic respiratory failure in obesity hypoventilation syndrome have been identified including physical activity, sleep quality and weight loss. These data have also established the potential clinical role of advanced physiological biomarkers of neural respiratory drive to monitor clinical change and to risk stratify patients during acute exacerbations of COPD. Finally, the data in this thesis provides further evidence that the major mechanism of action of home mechanical ventilation in hypercapnic COPD patients is the modification of central respiratory drive.

Statement of originality

I have been responsible for recruitment of all patients enrolled at St Thomas' Hospital and the Royal Brompton Hospital. I performed all of the experimental techniques described in this document on patients recruited from the above sites. Routine lung function testing was performed by the lung function department at the respective hospitals. Additional patients were recruited from Leeds and Aintree University Hospitals for the final study using actigraphy to investigate sleep disruption following initiation of non-invasive ventilation in COPD with raw actigraphy files transferred for analysis. Other clinical data for patients enrolled at Leeds and Aintree were collected locally and transferred on completed case record files.

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    - Sole funder of the Myotrace project (study 2) to investigate NRD during acute exacerbations of COPD.
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    - Joint funder of the HOT-HMV UK study (study 3) to investigate the role of HMV following acute hypercapnic exacerbations of COPD.

Abbreviations

95%CI	95% confidence interval
ABG	Arterial blood gas

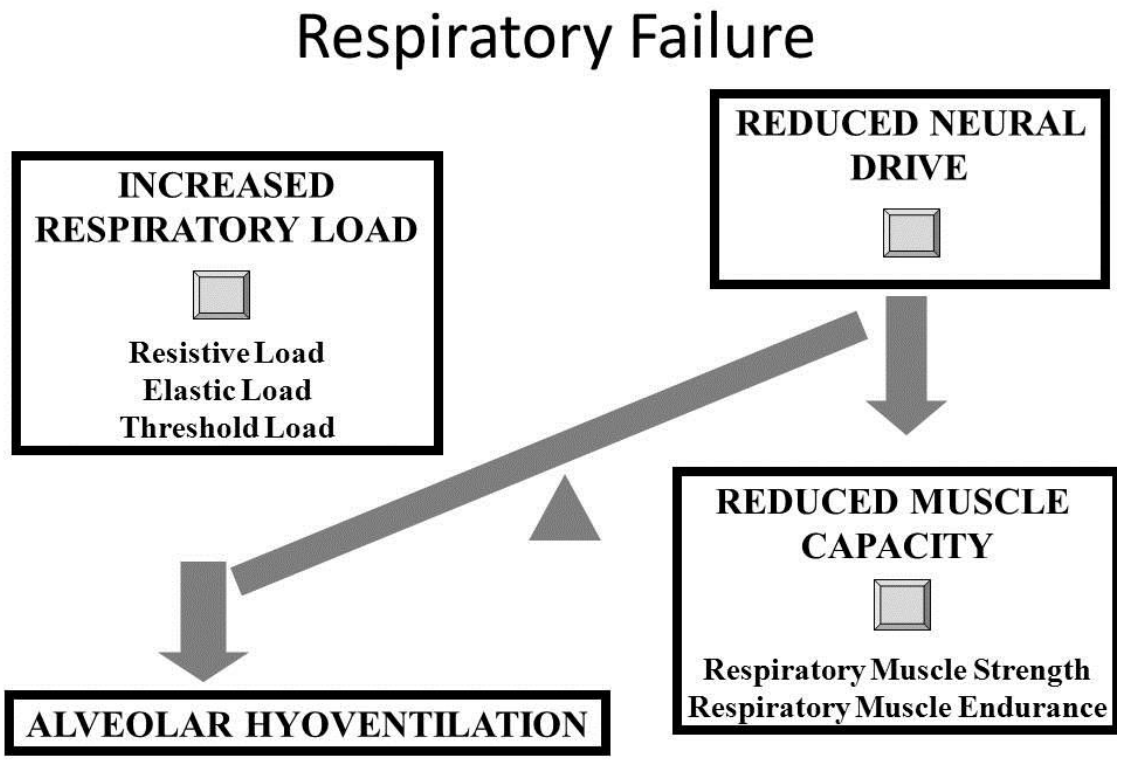
AHI	Apnoea-hypopnea index
AVAPS	Average-volume assured pressure support
BiPAP	Bi-level positive airway pressure
BMI	Body mass index
$C_{rs\ (dyn,\ stat)}$	Compliance of the respiratory system (dynamic, static)
Cv	Coefficient of variability
CaO_2	Oxygen content of arterial blood
COPD	Chronic Obstructive Pulmonary Disease
CPAP	Continuous positive airway pressure
CRQ	Chronic respiratory disease questionnaire
DLCO	Diffusion capacity of the lung for carbon monoxide
ECG	Electrocardiogram
$EMG_{(abdo,\ di,\ para,\ sc)}$	Electromyogram (of the abdominal, diaphragm, parasternal, sternocleidomastoid muscle)
EPAP	Expiratory positive airway pressure
ESS	Epworth sleepiness score
$etCO_2$	End-tidal carbon dioxide tension
FEV_1	Forced expiratory volume in 1 second
FFM	Fat free mass
FFMI	Fat free mass index
FSS	Fatigue severity score
FRC	Functional residual volume
FVC	Forced vital capacity
Hb	Haemoglobin
HCO_3^-	Bicarbonate
HCVR	Hypercapnic ventilatory response
HMV	Home mechanical ventilation
HOT	Home oxygen therapy
HOT-HMV UK	Home oxygen therapy versus home mechanical ventilation plus home oxygen therapy following an acute hypercapnic exacerbation of chronic obstructive pulmonary disease requiring non-invasive ventilation
HR	Heat rate
IC	Inspiratory capacity

ICS	Intercostal space
IPAP	Inspiratory positive airway pressure
ISWT	Incremental shuttle walk test
LTOT	Long term oxygen therapy
MEP	Maximum expiratory pressure measured at the mouth
MEWS	Medical early warning score
MIP	Maximum inspiratory pressure measured at the mouth
MRF-28	Maugeri Foundation respiratory failure questionnaire
NHS	National Health Service
NIV	Non-invasive ventilation
NMD	Neuromuscular disease
NRD	Neural respiratory drive
NRDI	Neural respiratory drive index
ODI	Oxygen desaturation index
OHS	Obesity hypoventilation syndrome
OSA	Obstructive sleep apnoea
$P_{0.1}$	Pressure 100ms after the start of inspiration
$P_{(aw, di, gas, oes)}$	Pressure (airway, transdiaphragmatic, gastric, oesophageal)
$PaCO_2$	Arterial carbon dioxide tension
PaO_2	Arterial oxygen tension
PCV	Pressure control ventilation
$_{(dyn)}PEEP_i$	Intrinsic positive end-expiratory pressure (dynamic)
PE_{max}	Pressure obtained during a maximum expiratory manoeuvre
PI_{max}	Pressure obtained during a maximum inspiratory manoeuvre
PS	Pressure support
PSG	Polysomnography
PSV	Pressure support ventilation
REM	Rapid eye movement sleep
RMS	Root mean squared
ROC	Receiver operating characteristics
RR	Respiratory rate
RV	Residual volume

SGRQ	St George's respiratory questionnaire
SNIP	Sniff nasal inspiratory pressure
SaO_2	Percentage oxygen saturation of haemoglobin in arterial blood
SF-36	Short form 36 questionnaire
SpO_2	Percentage oxygen saturation of haemoglobin in pulsatile blood
SRI	Severe respiratory insufficiency questionnaire
$T_{(i, e, tot)}$	$Time_{(inspiratory, expiratory, total\ respiratory\ cycle)}$
$tcCO_2$	Transcutaneous carbon dioxide tension
TLC	Total lung capacity
TwP_{di}	Transdiaphragmatic pressure obtained following phrenic nerve stimulation (twitch)
TST	Total sleep time
$V_{(A, DS, t, te)}$	Volume (alveolar, dead space, tidal, estimated tidal)
V_e	Minute ventilation
VAS	Visual analogue scale
WASO	Wake after sleep onset

The respiratory system maintains oxygen and carbon dioxide homeostasis, which is achieved with repetitive cyclical neural activation and subsequent contraction of the respiratory muscles. Contraction of the inspiratory muscles causes an increase in intrathoracic volume with a consequent decrease in intrathoracic pressure, which generates a subatmospheric pressure gradient causing airflow into the lungs. The efficiency of this respiratory muscle system is dependent on the strength and endurance of the respiratory muscles (*respiratory muscle capacity*) working against the resistance and compliance of the airways, lung and chest wall (*respiratory muscle load*). Respiratory failure arises due to an imbalance in the relationship between neural respiratory drive, respiratory muscle capacity and respiratory muscle load (Figure 1) and non-invasive ventilation (NIV) is used to augment alveolar ventilation in patients with chronic respiratory failure.

Figure 1: Respiratory muscle load-capacity-drive relationship



Illustrates the interaction between load, capacity and drive that is essential to produce ventilation

1.1: Assessment of Patients with Chronic Respiratory Failure

Few standards currently exist to guide the assessment of patients with chronic respiratory failure during the setup of home mechanical ventilation (HMV). Empirically, the evaluation of these patients requires little more than measurement of arterial blood gas tensions but, in practice, detailed physiological assessment of these key areas is often appropriate. A summary of current practice in evaluation has been divided into:

- Basic clinical assessment
- Gas exchange
- Overnight physiological monitoring
- Respiratory muscle function
- Neural respiratory drive
- Pulmonary mechanics
- Patient-ventilator interaction
- Health related quality of life
- Physical activity

1.1.1: Basic clinical assessment

The specific assessments in clinic consultations for patients will depend on the underlying aetiology of respiratory failure but a variety of issues are commonly identified regarding domiciliary ventilation and should be focused on to ensure that adequate patient-ventilator interaction and effective ventilation are achieved. The primary goal of the consultation should be for the clinician to demonstrate that the overall effect of HMV is acceptable to the patient and this can be judged by the adherence of the patient to the nocturnal prescription of NIV and by the effect with sustained use on arterial carbon dioxide tensions. The majority of home ventilators now have internal monitoring clocks that measure and record the total blower hours and/or data cards that can be used for the measurement of adherence. These data should be compared against

the patient reported adherence and any discrepancies investigated with the patient. Poor adherence should prompt further questioning to identify areas to improve compliance.

A range of clinical investigations are available to assist with the assessments of patients for HMV. These cover simple bedside tests to more complicated invasive testing used in research. The investigations are summarised below indicating those 'basic' tests (Table 1) used in routine clinical practice and 'advanced' procedures (Table 2) used in research.

Table 1: Basic investigations used in the assessment of home mechanical ventilation

Basic

Investigation	Unit	Assessment
Sniff nasal pressure (SNIP)	cmH_2O	Global inspiratory muscle strength
Maximum Inspiratory Pressure (MIP)	cmH_2O	Global inspiratory muscle strength
Maximum Expiratory Pressure (MEP)	cmH_2O	Global expiratory muscle strength
Spirometry (FEV_1/FVC)	l	Lung volume and airflow obstruction, VC an indirect measure of respiratory muscle strength
Cough Expiratory Flow	l/min	Global expiratory muscle strength
Arterial Blood Gases	Various	Gas exchange & acid base status

Table 2: Advanced investigations used in the assessment of home mechanical ventilation

Advanced

Investigation	Unit	Assessment
Sniff Oesophageal Pressure	cmH_2O	Global inspiratory muscle strength
Cough Gastric Pressure	cmH_2O	Global expiratory muscle strength
Sniff Trans-diaphragmatic Pressure (P_{di})	cmH_2O	Volitional diaphragm strength
Twitch P_{di}	cmH_2O	Non-volitional diaphragm strength
Intrinsic Positive End Expiratory Pressure	cmH_2O	Threshold load
Pulmonary Compliance	l/cmH_2O	Resistive load
Diaphragm $EMG_{\%max}$	%	Neural Respiratory Drive

1.1.2: Gas exchange

Arterial blood gas (ABG) analysis is an important tool in the assessment of patients receiving HMV. The test is simple to perform by skilled operators and the results are rapidly available allowing prompt clinical decisions. Many units are now using arterialised earlobe blood gas as an alternative to ABGs. These have been shown to accurately reflect the arterial partial pressure of carbon dioxide ($PaCO_2$) and can be less painful than the arterial equivalent.[1] However, earlobe blood gasses can poorly reflect the arterial partial pressure of oxygen (PaO_2), despite high correlation, due to wide limits of agreement tending to underestimate PaO_2 in the normal range and therefore need to be interpreted appropriately or used in conjunction with pulse oximetry.[2] A range of parameters can be measured by the modern blood gas analysis machines but those of most interest are the partial pressures of oxygen and carbon dioxide dissolved in the liquid component of blood (PaO_2 and $PaCO_2$, respectively) and the arterial bicarbonate (HCO_3^-) concentration. These parameters are used to define respiratory failure, which is divided into type 1, hypoxic respiratory failure ($PaO_2 < 8$ kPa) and type 2, hypercapnic respiratory failure ($PaCO_2 > 6$ kPa).

Oxygen

Oxygen delivery to the tissues is dependent on cardiac output and oxygen content of blood. Whilst the contribution of dissolved oxygen in blood to total oxygen content is small it is linked to haemoglobin saturation level and that contributes predominantly to oxygen content (CaO_2 = 1.34xSaO_2x[Hb] + 0.003xPaO_2). The correction of hypoxia with HMV is via a combination of improving hypoventilation, abolishing upper airways obstruction and alveolar recruitment. If there is additional intrinsic lung disease the addition of supplementary oxygen may be required to maintain adequate oxygenation. Whilst correction of daytime hypoxia has been shown to be beneficial in COPD[3] there is no clear randomised controlled trial evidence for the use of long term oxygen therapy (LTOT) in other diseases causing respiratory failure. In clinical practice, the same degree of hypoxia is used for non-COPD disease with LTOT prescribed when the PaO_2 < 7.3 kPa or with a PaO_2 < 8 kPa if there is evidence of sleep disordered breathing, cor pulmonale, right heart strain on the electrocardiogram and/or a haematocrit level greater than 50%.

Carbon dioxide

The main function of HMV is to correct nocturnal hypoventilation and therefore is given in the event of hypercapnic respiratory failure. In contrast to oxygen, the majority of carbon dioxide in arterial blood is dissolved in the liquid component rather than being protein bound. Due to the intrinsic properties of carbon dioxide, it rapidly crosses and equilibrates across the alveolar-capillary membrane and thus is inversely proportional to alveolar ventilation (V_A). V_A is a product of respiratory rate (RR) and the difference between tidal volume (V_t) and the physiological dead space (V_{DS}) [V_A = (V_t - V_{DS}) x RR]. Thus, hypoventilation can occur through increased dead space, decreased tidal volume or decreased respiratory rate. It is therefore possible to manipulate these variables using NIV, although one must appreciate that the ventilator circuit will produce a small increase in dead space. However, this is far outweighed by the significant improvements in tidal volume to enhance alveolar ventilation.

Acid-base balance

Acid-base balance is integrally linked to $PaCO_2$ homeostasis and the control of ventilation. Unlike hypoxia which directly stimulates ventilation via action of the carotid sinus, CO_2 mediates its effects on ventilation via alteration in intracellular pH detected by peripheral and central chemoreceptors. Chronic (via renal bicarbonate retention) and acute (via the Henderson-Hasselbach equation) hypoventilation cause a rise in HCO_3^- levels that aim to buffer the effect on pH of rising $PaCO_2$. The presence of respiratory acidosis ($pH < 7.35$) on blood gas analysis indicates an acute deterioration in respiratory failure that is yet to be compensated for and indicates the need for prompt treatment.

1.1.3: Overnight physiological monitoring

The investigations discussed so far allow the physician to understand the interaction between respiratory muscle load, respiratory muscle capacity and neural respiratory drive. However, this is directed to daytime measurements in the awake state for diagnosis of the clinical problem. The assessment of the respiratory physiological changes occurring during sleep that alter the respiratory muscle load, capacity, drive relationship are required to assess for nocturnal ventilatory support. There are a range of home and hospital systems, from simple to advanced, and these are used to:

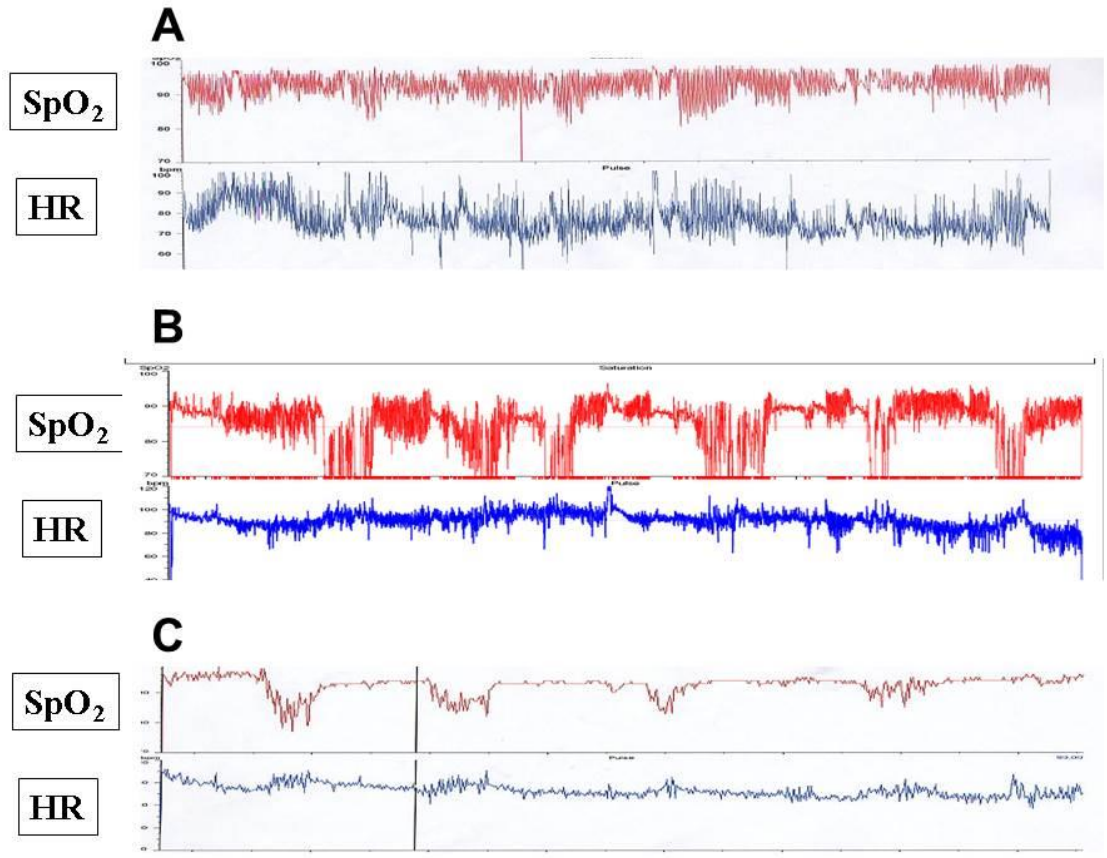
1. Diagnose sleep disordered breathing.
2. Assess the severity of the problem.
3. Monitor efficacy of treatment.

Oximetry

Overnight oximetry offers a simple, non-invasive and robust measure of nocturnal oxygenation and is a useful screening test in patients for the presence of sleep disordered breathing. Due to its ease and low cost it has been used extensively in obstructive sleep apnoea but is insufficiently sensitive to exclude a diagnosis in that condition.[4] The use of oximetry in the assessment of HMV can provide the clinician with valuable insights into the severity of disease and efficacy of treatment without requiring the patient to be admitted into hospital for full physiological monitoring studies and an experienced analyst can use these

simple studies to diagnose a range of more complex sleep disordered breathing.

Figure 2: Typical examples of oximetry tracings for [A] obstructive sleep apnoea, [B] obstructive sleep apnoea and hypoventilation, [C] isolated hypoventilation



Legend: Red, SpO_2; blue, heart rate.

Computerised scoring systems provide automated analysis producing a 4% oxygen desaturation index, analysis time spent with oxygen saturations <90% and heart rate variability that allow an indication of hypoxic load. There is limited evidence available to set a standard lower level of nocturnal oxygenation, although clinical practice would aim for a mean nocturnal oxygen saturation levels >88%.[5] Although these devices have widespread availability, the user should appreciate their limitations. These limitations are most noticeable when patients are receiving nocturnal oxygen therapy, resulting in a relatively normal oximetry trace as the hypoventilation and or upper airways obstruction may result in minimal changes in oxygen saturations. Oxygen

therapy acts to mask nocturnal desaturation by shifting the position on the oxyhaemaglobin dissociation curve to the right away from the steep portion. This means that substantially larger variations in ventilation are required to a produce a desaturation.

Transcutaneous capnography

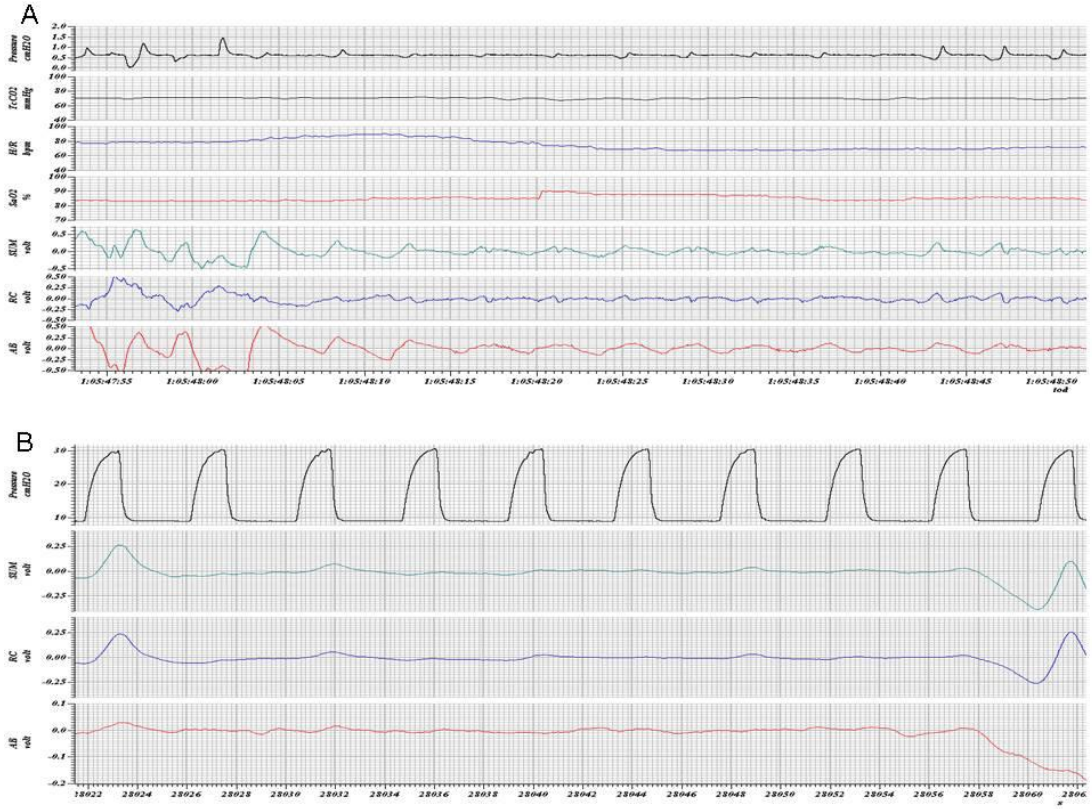
The hallmark of hypoventilation is an increase in $PaCO_2$. Immediately from sleep onset there is a reduction in tidal volume with an associated increase in $PaCO_2$ compared with wakefulness.[6, 7] This relative hypoventilation is further exaggerated at the onset of REM sleep due to the generalised muscle atonia.[8] Furthermore there is a degree of permissive hypercapnia with reduced central chemosensitivity to carbon dioxide that occurs during REM sleep.[9] Previously monitoring changes in CO_2 required either intermittent arterial sampling (sometimes via an indwelling line) or end tidal monitoring, the former is invasive and the latter unreliable in obstructive airways disease and during treatment with NIV. The measurement of expiratory CO_2 allows an accurate estimation of alveolar CO_2 which at the end of expiration has equilibrated with arterial blood and thus approximates to $PaCO_2$. However, in obstructive airways disease the prolonged expiratory phase often prevents the exhalation of alveolar gas and thus the measurement of end-tidal CO_2 becomes less accurate. The advent of robust and reliable transcutaneous CO_2 ($tcCO_2$) monitoring has allowed for improved analysis of nocturnal breathing disorders. The measurement of $tcCO_2$ is achieved electrochemically using a Severinghuas pH electrode to quantify the potentiometric difference between a reference and a measuring electrode. The resultant potential difference is proportional to the negative logarithm of $[CO_2]$. The technical constraints of the technique must be realised along with the appreciation that it is transcutaneous and not arterial values that are being measured. The measurements are taken using a heated electrode, allowing increased permeability of the skin to CO_2, facilitating measurement. The temperature settings will vary between systems but are usually in the order of 40-42^oC. This elevation in temperature causes an increase in the local $PaCO_2$ and combined with the fact that the skin is a metabolically active tissue, consuming oxygen and producing carbon dioxide, further increases the recorded value. The commercially available systems correct for this with an

automated algorithm that incorporates these factors and produces a value that should reflect actual $PaCO_2$. Clinical studies have shown $tcCO_2$ to reliably and reproducibly reflect $PaCO_2$ in a range of clinical situations and conditions including critical care and acute NIV as well as in sleep disordered breathing and obesity.[10-13] The introduction of combined pulse oximeter and $tcCO_2$ sensors has further increased the usefulness of these devices simplifying the amount of monitoring equipment necessary to study respiratory disorders during sleep. The sensors need to be intermittently re-membraned and calibrated at the beginning and end of use to ensure accuracy.

Advanced sleep studies

Full polysomnography is rarely required in the management of respiratory failure, although it can be useful if it is desired to elucidate the cause of persistent sleepiness despite therapy.[14] The use of transcutaneous carbon dioxide, nasal flow and respiratory inductance plethysmography allows full assessment of patients prior to initiation and during follow up and is sufficient in clinical practice. These modalities allow full respiratory sleep studies to be performed and the appropriate identification of complex sleep disordered breathing, differentiating an obstructive from a central apnoea and documenting hypoventilation as well as diagnosing periodic breathing abnormalities, such as Cheyne-Stokes respiration.

Figure 3: Examples of advanced sleep studies demonstrating [A] an obstructive apnoea and [B] a central apnoea occurring during non-invasive ventilatory support



Legend: Pressure, mask pressure; SUM, sum of chest and abdomen respiratory inductance plethysmography (RIP); RC, chest RIP; AB, abdominal RIP.

The differentiation of obstructive from central events is in a sense one of exclusion, being made by the absence of respiratory effort in the latter. This is routinely performed by respiratory inductance plethysmography to measure abdominal and thoracic excursion. The technique is widely accepted and is well tolerated by patients and easy to perform, however it may over diagnose central events.[15] Respiratory sleep studies are also helpful in initial titration of NIV settings and diagnosing synchronisation issues between the patient and the ventilator as well identifying common events, such as ventilator autocycling and trigger delay.

1.1.4: Respiratory muscle testing

Respiratory muscle weakness can be a cause of unexplained breathlessness with classical symptoms of diaphragm paralysis including orthopnoea, breathlessness in water and breathlessness on exercise.[16, 17] Although routine imaging techniques may raise the suspicion of diaphragm paralysis the

sensitivity and specificity of these tests are poor and should not be relied upon to make a diagnosis.[18] Profound respiratory muscle weakness initially leads to nocturnal hypoventilation prior to diurnal hypercapnia becoming established and this may be used as an early detector of need for nocturnal ventilatory support in at risk populations.[19, 20] Tests of respiratory muscle strength are used in the diagnosis of unexplained hypercapnic respiratory failure and abnormalities require further testing to ascertain whether there is a generalised systemic neuromuscular problem or whether it is isolated to the diaphragm. The latter can often be a consequence of neuralgic amyotrophy. Isolated unilateral or bilateral diaphragm weakness can produce sleep disordered breathing but usually requires the presence of another pathological process in order to cause respiratory failure requiring NIV.[21-23]

Non-invasive

A simple test of respiratory muscle strength is change in VC from sitting to supine. However, other more specific tests, including SNIP and MIP are available that better predict the presence of sleep disordered breathing and need for NIV, particularly in patients with NMD.[19, 24] Both these pressure measurements can be performed using handheld devices with a nasal bung or mouth piece, respectively. Sniff nasal inspiratory pressure (SNIP) and mouth inspiratory pressure (MIP) reflect overall respiratory muscle strength and are generally performed from FRC. Although the early literature reported that MIP testing should be performed from residual volume (RV)[25] more recent work has shown that it is reasonable to simplify the procedure by measuring peak pressure from FRC.[26] Previous work has shown good correlation between airway pressure (P_{aw}) and oesophageal pressure (P_{oes}) during sniff manoeuvres in patients without significant airways obstruction.[27] Due to the wide normal range of MIP values and the technical difficulty some patients have with performing the procedure, particularly those with bulbar dysfunction, SNIP may provide a better method of excluding significant respiratory muscle weakness without the need for invasive testing.[28] Although providing a reliable assessment of respiratory muscle function in patients with bulbar dysfunction[19] it should be realised that SNIP also has its limitations, in particular in COPD when airflow obstruction can prevent rapid equalisation of pressure between the

alveoli and upper airway giving a falsely low reading.[29] However, multiple tests to assess respiratory muscle strength are required to exclude weakness in symptomatic patients.[30, 31] Details on the test protocols can be found in the European Respiratory Society and American Thoracic Society statement on respiratory muscle testing.[32]

Due to the passive nature of expiration normally the focus of respiratory muscle testing is usually on the inspiratory muscles. Expiratory muscle function may be assessed non-invasively using maximum expiratory pressure (MEP) with pressure measured at the mouth in an analogous fashion to MIP during a forced expiration (from TLC) manoeuvre. It is important to prevent the subject from using buccal manoeuvres to alter the mouth pressure. As with MIP, MEP has a wide normal range meaning low readings should be interpreted within a clinical evaluation. Other simple and commonly used tests of the expiratory muscles include cough peak expiratory flow (cough PEF) and whistle P_{mo}. If invasive assessment of the expiratory muscles is being performed a voluntary cough P_{gas} is measured to assess muscle function or if involuntary assessment is required a twitch T10 can be recorded.

A cough PEF can be performed using a standard peak flow meter attached to a face mask and usually requires little or no coaching to produce acceptable technique. It must be realised that although this test indicates expiratory muscle performance the pressure and force generated depends on lung volumes and coordinated bulbar function to rapidly open and close the glottis during cough pressure generation and release. Therefore, values obtained will be reduced in patients with inspiratory muscle weakness due to inability to perform deep inspiration prior to cough initiation and in those patients with bulbar dysfunction as well as those with true expiratory muscle weakness.[33] Patients with a cough PEF <180 ml/min have been shown to be unable to independently clear secretions.[34] These patients can augment cough response with manual physiotherapy and using insufflation-exsufflation devices[35] and this augmented cough level is associated with improved prognosis independent of VC or breathing pattern.[34]

The normal ranges for voluntary respiratory manoeuvres are provided in Table 3.

Table 3: Normal ranges for voluntary respiratory muscle manoeuvres

	Male (cmH_2O)	Female (cmH_2O)
$Sniff_{Pdi}$	148 ± 24	122 ± 25
SNIP	105 ± 24.5	94 ± 21
MIP (FRC)	106 ± 22	87 ± 21
MIP (RV)	114 ± 27	88 ± 18

Units given as cmH_2O and are mean±SD. Abbreviations: P_{di} – transdiaphragmatic pressure, SNIP – sniff nasal inspiratory pressure, MIP – mouth inspiratory pressure, FRC – functional residual capacity, RV – residual volume. Data adapted from [28, 36].

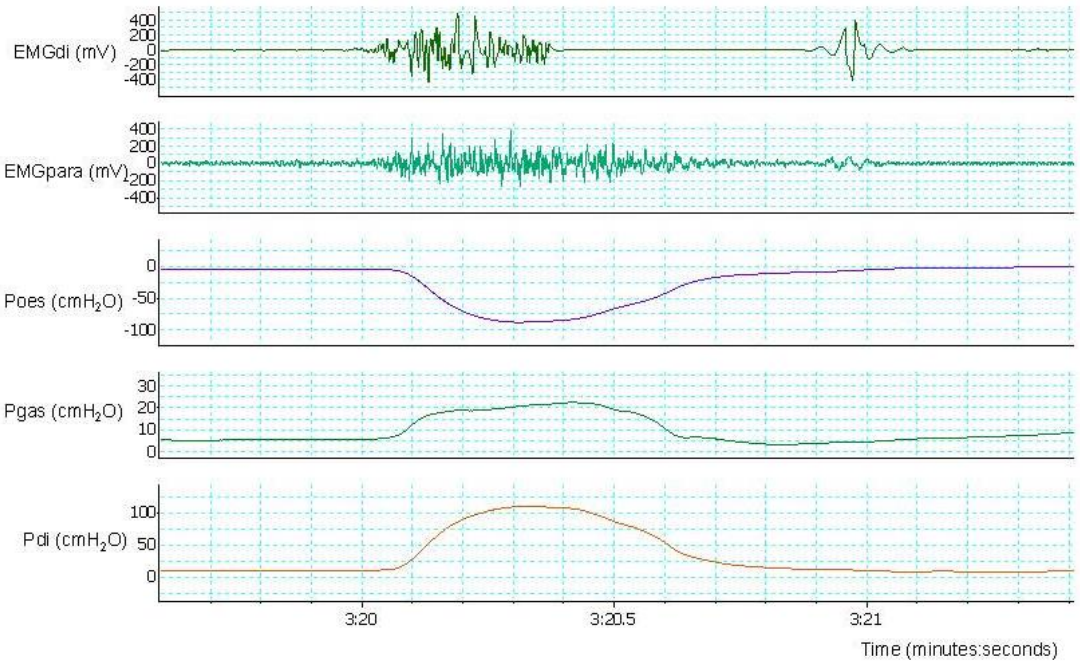
Invasive

As both SNIP and MIP are volitional tests, a low value does not necessarily indicate inspiratory muscle weakness but could represent inadequacy in performing the test. Therefore, if the non-invasive testing value is equivocal or a more accurate assessment is needed, invasive respiratory muscle testing can be performed. These require both a technically skilled operator as well as more specialised, but commercially available, equipment. Testing requires the insertion of oesophageal catheters to measure P_{oes} and EMG_{di} and a gastric catheter to measure gastric pressure (P_{gas}). For these reasons, these tests are usually performed in tertiary specialist units.

Voluntary manoeuvres are performed with maximal sniff efforts, ($Sniff_{Poes}$ and $Sniff_{Pdi}$) and maximal cough effort ($Cough_{Pgas}$) recorded via data acquisition software (Figure 4). The pressures generated will, in part, be affected by lung volumes and this should be taken into account when analysing the results. Although $Sniff_{Pdi}$ specifically measures diaphragm function it cannot assess hemi-diaphragm function and in order to do so isolation phrenic nerve stimulation must be performed. Currently, this is performed using magnetic rather than electrical phrenic nerve stimulation as it is better tolerated and easier to perform.[37, 38] The measurement of transdiaphragmatic pressure following supramaximal phrenic nerve stimulation (TwP_{di}) is the gold standard for demonstrating unilateral (Figure 5) or bilateral diaphragm weakness; normal

ranges for phrenic nerve stimulation are provided in Table 4. Furthermore, diaphragm activation can be stimulated centrally via transcranial magnetic stimulation.[39-41] This allows accurate measurement of nerve conduction time, central and peripheral diaphragm fatigue, EMG_{di} latency and amplitude as either compound muscle action potential or motor evoked potential. These measurements are generally used as research tools, although these detailed assessments are required for the evaluating patients for intramuscular diaphragmatic pacer insertion.[42]

Figure 4: Voluntary sniff manoeuvre



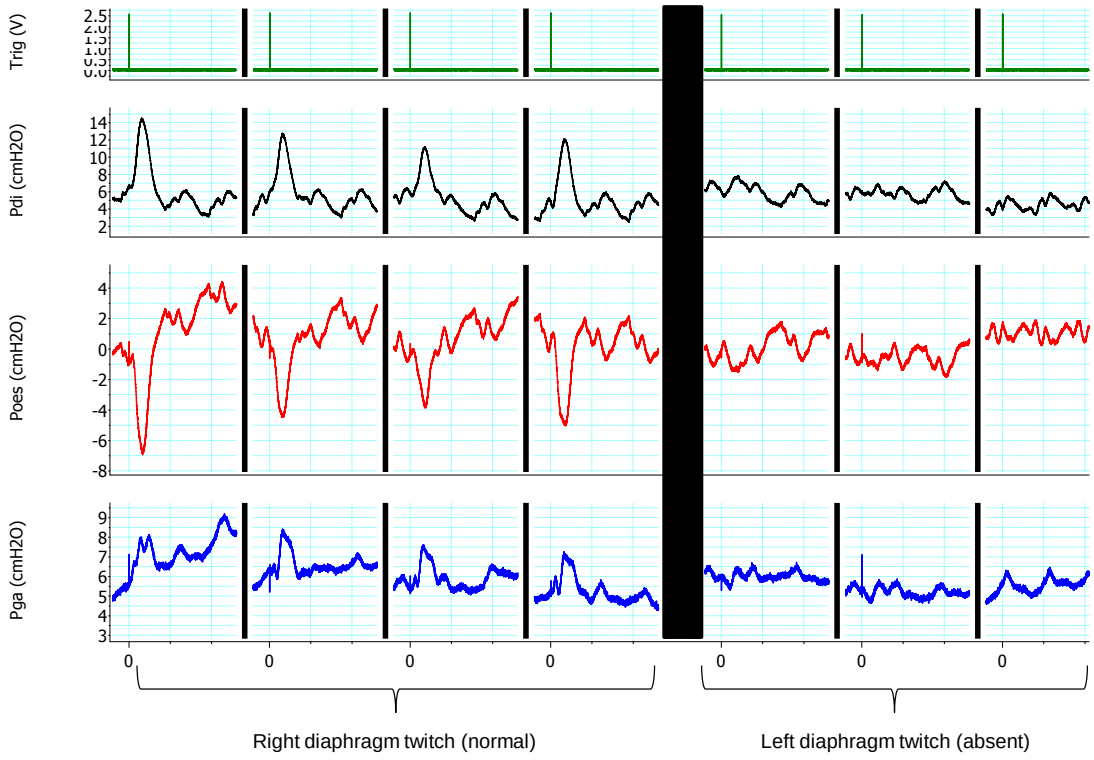
A set of traces showing a maximum sniff manoeuvre in a healthy volunteer with coordinated activity of diaphragm and parasternal muscles preceding respiratory system pressure changes. Figure shows diaphragm EMG (EMGdi) parasternal EMG (EMGpara) oesophageal pressure (Poes), gastric pressure (Pgas) and transdisphragmatic pressure (Pdi). All pressure traces are shown in cmH_20 and EMG traces in mV after amplification (x1000).

Table 4: Normal ranges for twitch diaphragmatic pressure (TwPdi) performed by magnetic stimulation

	Pressure (cmH_2O)
Bilateral TwP_{di}	21 ± 5
Left TwP_{di}	11 ± 2
Right TwP_{di}	8 ± 2

Units given as cmH_2O and are mean ± SD. Data adapted from [43-45].

Figure 5: Left hemi-diaphragm paralysis on invasive testing



A set of traces demonstrating left hemidiaphragm paralysis on invasive muscle testing with absent P_{di} following left phrenic nerve stimulation. Traces show time of magnetic discharge (trig), transdiaphragmatic pressure (TwP_{di}), oesophageal pressure (P_{oes}) and gastric pressure (P_{gas}). All pressure traces are shown in cmH_20.

1.1.5: Neural respiratory drive

The measurement of NRD *in vivo* is difficult to assess and has be estimated using a number of techniques. The motor output from the respiratory centre itself cannot be directly quantified and so surrogate markers are used instead. Most simply, ventilation has been used as an estimate of NRD but is of little use in disease states as it is affected by the mechanics of the respiratory system. Measures of respiratory muscle performance have also been tested but again are limited due to the influence exerted by respiratory system mechanics.[46] The assessment of respiratory muscle activity using electromyogram (EMG) to

estimate NRD has been employed in both healthy subjects and COPD patients.[47, 48] Early work concentrated on the diaphragm EMG (EMG_{di}) and although this does not represent neural output to the entire of the respiratory muscle pump, the diaphragm is the principal respiratory muscle accounting for the majority of the work of breathing in healthy individuals.[49] EMG_{di} has been assessed using both surface and oesophageal electrodes. The use of surface electrodes to record EMG_{di} is problematic due to the proximity of the abdominal muscles which can induce significant cross-talk.[50, 51] The use of surface electrodes quantifies costal rather than crural diaphragm activity and the contribution of each to respiratory activity, whilst highly correlated, continues to be the subject of debate.[52] EMG_{di} measured using an oesophageal electrode has been used to quantify NRD in many diverse clinical settings including in COPD,[53] obesity,[54] cystic fibrosis[55] and critical care.[56] Changes in lung volume alter the resting length the respiratory muscles and thus can alter the length-force relationship, this is particularly true of the diaphragm.[57] However, despite the initial concerns with regard to changes in EMG_{di} signal with changes in lung volume, recent studies have shown the reliability and reproducibility of this technique using multi-pair recording electrodes.[53, 58] The use of EMG_{di} allows for quantification of NRD during resting breathing, by relating tidal values to the peak EMG recorded during a maximum inspiratory manoeuvre,[53] and during hypercapnic challenge testing.[59]

Respiratory drive may also be assessed from the pressure developed during the first 100ms of inspiration ($P_{0.1}$).[60] Whilst initially thought to accurately reflect respiratory motor output and be unaffected by pulmonary mechanics and respiratory pattern it is now appreciated that it is governed by the force-length relationship of the diaphragm, such as occurs in hyperinflation.[61] It is therefore often considered using a ratio of the $P_{0.1}$ during tidal breathing to that produced during a maximum inspiratory manoeuvre ($P_{0.1}$:$P_{0.1max}$). Unlike metabolic changes, pulmonary mechanics or respiratory muscle strength, changes in $P_{0.1}$ have been shown to explain the variance in dyspnoea in individual patients with COPD during hypercapnic ventilatory response and exercise testing, demonstrating the importance of respiratory drive on the perception of breathlessness.[62]

1.1.6: Pulmonary mechanics

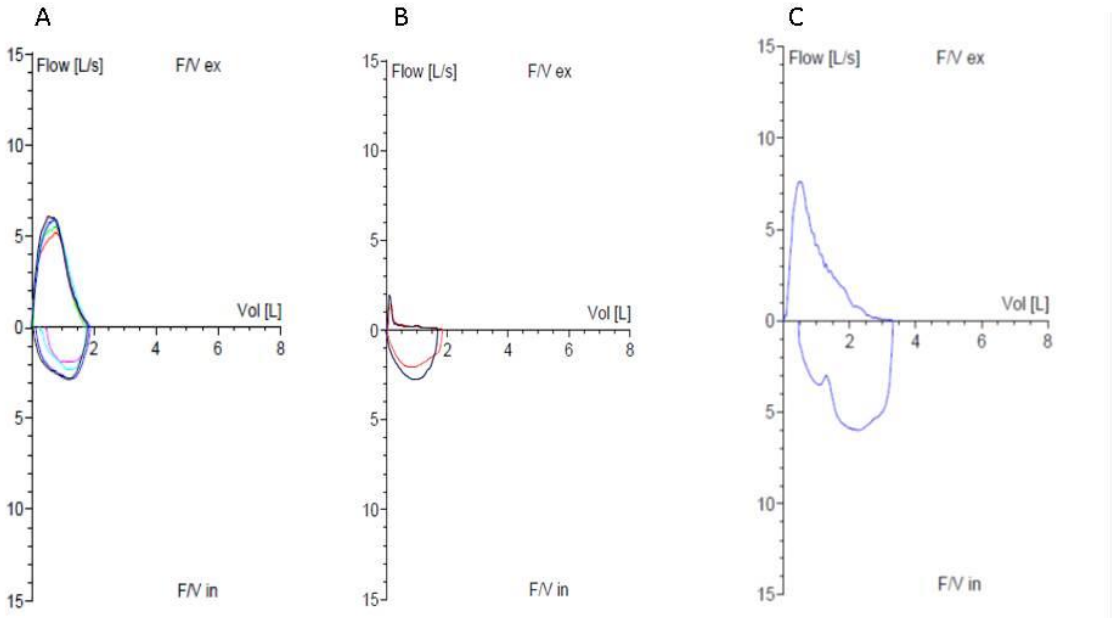
A clear understanding of pulmonary mechanics is essential for the physician to enable optimal individualised ventilator settings to be prescribed for the patient. Assessment of pulmonary mechanics ranges from basic spirometry, which can be routinely used in bedside testing and in clinics with portable meters, to full lung function testing with measurements of static and dynamic compliance. The interpretation of respiratory function abnormalities are summarised below with particular reference to HMV. Common patterns of spirometry are found in patients requiring HMV with the typical lung function abnormalities found in COPD, obesity and neuromuscular disease summarised in Table 5 and Figure 6_{A-C}.

Table 5: Typical results of lung function tests in home mechanical ventilation population

	COPD	NMD	Obesity
FEV_1	-	N / -	N / -
FVC	-	N / -	N / -
FEV_1/FVC	-	N / +	N / +
TLC	+	N / -	N / -
RV	+	-	N / +
RV/TLC	+	N / +	N / +
DLCO	-	-	N / -
KCO	N / -	N / +	N / +
MIP	N / -	-	N
MEP	N	-	N

Legend: N, normal; -, decreased; +, increased. Abbreviations: FEV_1 – forced expiratory volume in 1s, FVC – forced vital capacity, TLC – total lung capacity, RV – residual volume, DLCO – diffusion capacity of carbon monoxide, MIP – mouth inspiratory pressure, KCO – diffusion capacity corrected for alveolar volume, MIP – maximum inspiratory pressure, MEP – maximum expiratory pressure.

Figure 6: Flow volume loops from patients with [A] neuromuscular disease, [B] Chronic Obstructive Pulmonary Disease and [C] obesity



A - Neuromuscular disease (myotonic dystrophy) showing reduced lung volumes and without airway obstruction.
B - Chronic obstructive pulmonary disease showing a typical concave expiratory loop indicating airways obstruction.
C - Obesity revealing mildly reduced lung volumes with some concavity of the expiratory loop consistent with early airway closure.

Lung volumes

The pattern of change of lung volumes depends on the underlying disease with hyperinflation occurring in COPD and reduced lung volumes in obesity and restrictive thoracic disorders, such as chest wall disease and neuromuscular disease. Functional residual capacity (FRC) is the point at which outward elastic recoil of the chest wall balances inward recoil of the lungs. A change in FRC may move the patient to an inefficient position on the pressure-volume curve increasing work of breathing.[63, 64] FRC can be measured via a number of techniques including helium dilution, nitrogen washout and arithmetically from whole body plethysmography. Each have potential advantages and disadvantages but, in clinical practice, the methods produce similar results except when there are large areas of unventilated lung as is the case in some patients with bullous emphysema.[65] Usually the differences are only important when conducting research or considering specialised therapies such as lung

volume reduction surgery. It is important to recognise that true FRC can only be measured with the respiratory muscles relaxed. This may not be the case in patients with advanced COPD in whom measured FRC may be falsely elevated.[66]

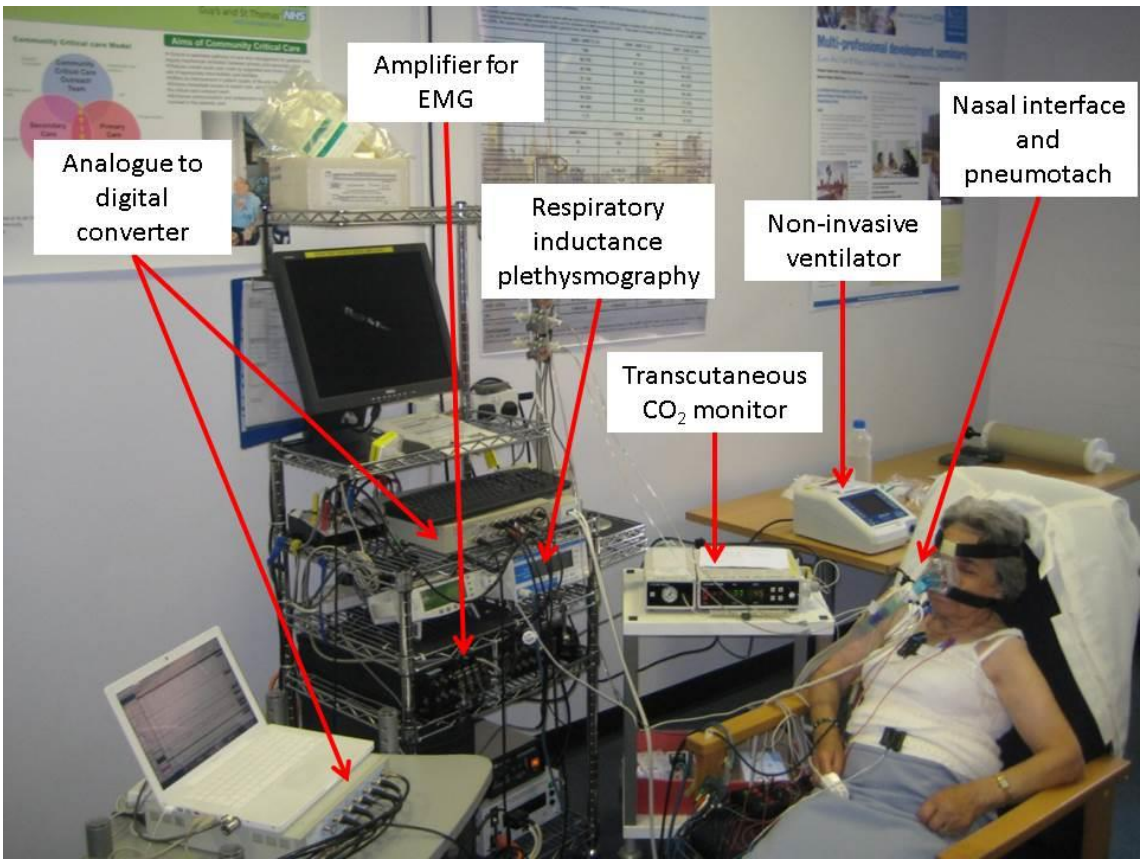
Basic spirometry, used to measure forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC), is the most commonly encountered measure of pulmonary mechanics and is used to monitor progression of a range of diseases including COPD and is useful in predicting survival in neuromuscular disease, including amyotrophic lateral sclerosis.[67] A fall in FVC of greater than 20% from sitting to supine is abnormal and may indicate significant diaphragmatic weakness.[23, 68] However, because of the non-linear relationship between volume and pressure, tests of respiratory muscle strength that measure the pressure generated by the respiratory muscles are a more sensitive marker of declining respiratory function than the measurement of lung volumes.[19, 69] In clinical practice, this will include sniff inspiratory nasal pressure (SNIP) and maximal inspiratory pressures (MIP) measured at the mouth, which are discussed in the *Respiratory Muscle Testing* section of this chapter (page 39).

Advanced physiological measurements

The detailed measurement of pulmonary mechanics requires the use of specialist equipment and skills (Figure 7) and has become less common in routine clinical practice. The basic mechanics of the respiratory system is the action of respiratory muscles to produce negative intrathoracic pressure changes that result in airflow. To study this phenomenon requires the measurement of pressure changes throughout the system and the flow generated. This is most commonly achieved with the use of differential pressure transducers and a pneumotachograph, the signals from these devices are amplified and converted from analogue to digital signals and presented by commercially available software packages. Once digitised the signals can be later manipulated and studied to measure pulmonary mechanics. As pleural pressure cannot usually be measured directly,[70] mid-oesophageal pressure is used as a surrogate marker and is measured with an oesophageal balloon catheter inserted per-nasally.[71] Pressure measurements are also acquired from

gastric balloon catheters, to determine transdiapragmatic pressure, and at the mouth in order to calculate the transpulmonary pressure. The use of oesophageal catheters also allows the measurement of the diaphragm electromyogram (EMG_{di}) without the disadvantages of poor signals acquired from surface electrodes, this is commonly now performed using a single combined catheter to ease patient comfort.[52]

Figure 7: Patient attending for advanced physiological monitoring



A patient attending for physiological evaluation including measurement of respiratory muscle strength, neural respiratory drive and pulmonary mechanics on and off non-invasive ventilation. Illustrates the range of equipment needed for specialist invasive testing.

Compliance

Compliance of the respiratory system (C_{rs}) reflects the ease with which pressure changes produced by the respiratory muscles change the volume of the lung. It is defined as the change in lung volume per unit change in pressure across the respiratory system. In obese patients, for example, the C_{rs} can be reduced thus meaning the lungs are more difficult to inflate and such patients require higher levels of pressure support to ensure adequate ventilation.[66, 72-74] Patients with neuromuscular disease often have a normal or slightly reduced lung and chest

wall compliance,[75-77] however, due to the loss of muscle mass and thus the overall compliance of the respiratory system is often preserved. Therefore these patients can usually be ventilated easily at lower pressures.

Compliance can be measured as a static or dynamic measure, each providing useful physiological data and both having advantages and disadvantages. The measurement of static compliance (C_{stat}) requires the use of specialised equipment, including a body box for plethysmography, and relies on the ability of the patient to completely relax their respiratory muscles and make no respiratory effort, as the measurements are taken at zero flow to exclude airway resistance. This is, in practice, difficult to achieve in spontaneously breathing patients. Although modified techniques exist to measure C_{stat}, such as rapid airway occlusion, these are still limited in the clinical setting.[78] However, dynamic compliance (C_{dyn}), can be achieved easily in spontaneously breathing patients, although like C_{stat} measurements, it does require the insertion of a balloon catheter to measure oesophageal pressure (P_{oes}) and rests on the assumption that the respiratory muscles are inactive at the point of zero flow. The patient simply performs resting breathing through a pneumotachograph with an oesophageal balloon *in situ*. The integration of the flow from the pneumotachograph provides a value for V_t and this is divided by the pressure change between end inspiration to end expiration (ΔP_{oes}). Values are averaged over five to ten stable breaths. The pressure changes are taken from zero flow at end inspiration and end expiration as this should represent points of complete relaxation of the respiratory muscles. During inspiration, a proportion of the pressure produced by the respiratory muscles is to overcome surface tension and airways resistance and thus C_{dyn} is measured in the relaxed expiratory phase. The main limitation of C_{dyn} is that it can be inaccurate in obstructive lung disease as there remains intrapulmonary airflow at end of inspiration. Furthermore, the value is falsely reduced in patients with tachypnoea.[79]

Positive end-expiratory oesophageal pressure

$PEEP_i$ occurs due to airflow limitation resulting from the narrowing of airways with resultant residual positive pressure in the alveolus, and so also the pleural pressure, at the end of expiration. This results in an increase in the work of breathing and has a negative impact on ventilator triggering. Whilst it is not

often measured in the HMV population and is more pertinent in acute ventilation in critical care, knowledge of the concept can enhance patient set up for HMV. The presence of $PEEP_i$ can occur due to a range of processes including:

1. Insufficient expiratory time to allow pressure equalisation across lung units due to airway obstruction e.g. COPD.[80]

2. Dynamic airway collapse causing flow limitation e.g. emphysema or obesity.[54]

3. Pulmonary oedema due to cardiac dysfunction.

Both static and dynamic $PEEP_i$ can be measured and requires the use of oesophageal balloon catheter and a pneumotachograph, similar to the measurement of compliance. For the measurement of static $PEEP_i$ airway occlusion is required at the end of passive expiration. The resultant plateau pressure represents the average $PEEP_i$ across the whole lung and may vary considerably between lung units in disease processes associated with profound heterogeneity e.g. emphysema. Active expiration will cause a falsely high value and patients should be coached to avoid this phenomenon.[81] Dynamic $PEEP_i$ can be measured in the spontaneously breathing patient without the need for airway occlusion. The P_{oes} at the end of expiration at the point of zero flow represents the lowest level of $PEEP_i$ within the lung that is required to be overcome in order to instigate flow. This can therefore be substantially lower than static $PEEP_i$, most notably in those with airflow obstruction. If active expiration occurs this can be partly compensated for by subtracting the change in gastric pressure (ΔP_{gas}) from the value of $PEEP_i$ calculated.[66, 80] In the clinical setting failure to correctly titrate EPAP high enough to match patients $PEEP_i$ can lead to increased work of breathing, discomfort and triggering problems, especially in the acute setting.[82] Equally an EPAP set too high can worsen gas trapping and again lead to patient-ventilator dysynchrony. $PEEP_i$ depends on underlying disease and, in general, it is usually absent in neuromuscular disease, but can be a significant problem in patients with both obstructive airways disease and obesity.[83] Significant PEEP occurs in obese patients in the supine position due to the pressure exerted by the abdominal contents and therefore the position of the patient during measurements must be

taken into consideration when interpreting measured PEEP values and setting EPAP.[54] It must also be noted that EPAP is used to abolish upper airway obstruction and maintain airway patency if there is coexistent obstructive sleep apnoea.

Work of breathing

In the normal state, the respiratory system consumes a small proportion of the total oxygen consumption, typically less than 5%, but in illness this can rapidly escalate to more than 30% of the total. Whilst rarely measured in a clinical setting unloading the respiratory muscles and reducing work of breathing has been shown to be associated with improved ventilator comfort and can be used to compare the effectiveness of modes of ventilation.[84] Again, measurements are taken during spontaneous breathing using a balloon catheter to measure P_{oes} and a pneumotachograph with the integration ΔP_{oes} between points of zero flow generating the pressure-time product, which correlates with oxygen consumption and metabolic work of breathing.[85] This technique can show changes in work of breathing against changes in respiratory load but with the addition of assisted ventilation it can be difficult to interpret as the changes in P_{oes} represent, in part, the work performed by the ventilator rather than respiratory muscles.[84] To accurately measure changes in work of the respiratory muscles during ventilation either change in oxygen consumption from spontaneous breathing to assisted breathing can be measured or the respiratory muscle activity can be measured using the diaphragm electromyogram (EMG_{di}). These methods allow the physiological effects of modes of ventilation to be compared in detail as well as providing insights in to the pathological processes involved in patients requiring HMV. Patients with high work of breathing during spontaneous respiration include those with COPD and obesity due to the high load on the respiratory system imposed by either airflow obstruction and hyperinflation or low chest wall and abdominal compliance. Patients with neuromuscular disease, if no other disease process is present, have a low work of breathing and consequently require lower levels of respiratory support.

1.1.7: Patient-ventilator interaction

The principal areas that need assessment include:

1. *Interface* - mask leak, mouth leak, mask seal, head gear, mask and head gear condition and skin pressure areas.

2. *Trigger efficiency* – inspiratory and expiratory synchronisation, frequency of autocycling, frequency of prolonged inspiratory support.

3. *Pressurisation* – symptoms of daytime hypersomnolence and headache, worsening breathlessness, continued snoring and signs of cor pulmonale, excess or inadequate pressure delivered.

Sufficient time must be allowed during the initial set up of NIV to individualise the ventilator settings. Furthermore, regular follow up must be undertaken to assess adherence to, and efficacy of HMV as a failure to improve gas exchange or poor compliance may represent patient-ventilator dysynchrony, progression of the underlying disease or ventilator malfunction. The use of physiological targeted set up, using invasive measures of pulmonary mechanics to obtain NIV settings that maximally unload the respiratory muscles, has been reported by some investigators to improve patient comfort and enhances patient-ventilator interaction.[82, 84] Whilst some patient-ventilator interactions can be assessed clinically others require the use of more invasive physiological testing to assess a problem.

1.1.8: Health related quality of life

The assessment of health related quality of life (HRQL) has become of increasing importance in modern healthcare. These assessment tools can be generic, disease specific or treatment specific. The use of generic tools allows the comparison between groups of patients with different diseases but may lack the sensitivity to detect changes in important symptoms in specific populations.[86] Several questionnaires have been used to measure health related quality of life in patients with chronic respiratory failure, such as the Chronic Respiratory Questionnaire (CRQ) and St George's Respiratory Questionnaire (SGRQ).[87, 88] However, these questionnaires were derived for patients with obstructive pulmonary disease and so may not be applicable in patients from other diagnostic groups such as obesity hypoventilation syndrome (OHS). Two questionnaires have been validated for measuring health related quality of life in patients with chronic respiratory failure receiving domiciliary

ventilation: the Severe Respiratory Insufficiency (SRI) questionnaire and the Maugeri Foundation Respiratory Failure (MRF) -28 questionnaire.[89-91] These questionnaires have been shown to be responsive to changes occurring following the treatment of chronic respiratory failure with HMV.[92, 93]

1.1.9: Physical activity

The assessment of physical activity has previously been limited to subjective self-reported assessments[94] or formal exercise testing, such the incremental shuttle[95] and 6 minute walk tests.[96] Recent technological advances have allowed the objective measurement of daily physical activity using sensitive motion sensors (actigraphs)[97] and the estimation of free living energy expenditure.[98] Actigraphy involves the use of accelerometers to measure movement and was initially used to assess the sleep-wake cycle in circadian rhythm disorders.[99, 100] The devices are usually worn on the wrist when assessing sleep but may be worn on the wrist, arm or hip when assessing physical activity.[101] In the assessment of patients with chronic respiratory failure using domiciliary NIV, actigraphy enables both the objective measurement of physical activity as well as the sleep-wake cycle.

The importance of exercise capacity and physical activity in chronic respiratory failure is underlined by the prognostic information carried by these assessments. Objectively quantified physical activity has been shown to be a strong predictor of all-cause mortality in COPD.[102, 103] The 6 minute walk test can be used in patients with chronic respiratory failure undergoing HMV to stratify mortality with the worst outcomes in those with the most impaired exercise performance.[104] This relationship is most pronounce in patients with COPD in whom skeletal muscle dysfunction is secondary to reduced physical activity,[105] whereas it is of less prognostic value in OHS in whom exercise capacity is relatively preserved.[104] The administration of HMV in chronic respiratory failure has been shown to improve exercise capacity independently of changes in peripheral muscle function.[106] The use of actigraphy has become increasingly common and has been shown to accurately reflect physical activity during household chores and metabolic activity in patients with chronic respiratory failure[107, 108] and thus is a patient relevant outcome. Furthermore, in patients with COPD low levels of physical activity following an acute

exacerbation have been shown to indicate an increased risk of subsequent readmission, demonstrating the important clinical relevance of this endpoint.[109]

Due to the strong prognostic link, much of the current evidence relates to the use of NIV in COPD related respiratory failure. HMV has been shown to improve exercise capacity as part of a structure long term rehabilitation programme.[110, 111] The study by Duiverman and colleagues examined the effects of the addition of HMV to pulmonary rehabilitation in patients with COPD and chronic respiratory failure at 1 and 2 year intervals in a randomised controlled study. The primary outcome of the study was HRQL, which showed no significant change in the CRQ, a general measure of HRQL but improvement in the MRF-28, a HMV specific measure. However, the study did show improvement in exercise capacity, measured by the 6 minute walk test, and physical activity, measured by step count in the HMV group. In addition to the use of HMV to improve exercise capacity in COPD NIV has been implemented during exercise and recovery to augment the training response. The rationale for this application is that high work of breathing contributes to dyspnoea and limits exercise performance in severe COPD.[112, 113] The addition of NIV during exercise in COPD improves walking distance and decreases dyspnoea.[114, 115] However, there are practical considerations that can limit its utility and thus it remains controversial.[116]

The importance of physical activity in obesity is empirically clear with the limitation to exercise capacity in such obese subjects being multifactorial.[117, 118] A significant contributor to exercise limitation in obesity relates to altered pulmonary mechanics.[74, 119] Although there have been few data to support improvements in exercise capacity induced by HMV in OHS small studies have demonstrated the ability of NIV to augment patients performance during symptom limited exercise testing.[120] In addition to the potential for physical activity to augment weight loss in patients with OHS it may in itself improve sleep disordered breathing.[121] Despite the important link between physical activity and obesity no data yet exists to measure the extent of inactivity in obesity hypoventilation syndrome or the changes that occur following domiciliary NIV.

1.2: The Role of Domiciliary Non-Invasive Ventilation in Chronic Respiratory Failure

1.2.1: From the Polio epidemic to the obesity epidemic

The ability to support patients with ventilatory failure without the need for invasive ventilation has been one of the major advances of respiratory medicine in recent times. NIV initially developed as part of critical care for use within the intensive care unit but has quickly progressed to be used in specialised respiratory units and in the community for a range of pathologies culminating in respiratory failure. Whilst used in critical care to support acute respiratory failure technological advances from negative to positive pressure ventilation and improvements in patient interfaces have facilitated the use of this technology within the domiciliary setting for patients with chronic hypercapnic respiratory failure. The initial clinical demand for application of this technology was in neuromuscular disease, particularly following acute poliomyelitis, however, subsequent changes in demographics have led to other aetiologies rising in predominance. Domiciliary NIV is now provided for hypercapnic respiratory failure associated with both OHS and COPD. Although these syndromes have a common end process, chronic respiratory failure, this develops as a consequence of differing pathophysiological mechanisms and this has implications for patient assessment and ventilator set up.

1.2.2: Evidence for domiciliary non-invasive ventilation in neuromuscular disease

Early studies showed that the majority of patients with progressive neuromuscular disease die due to respiratory failure.[122] This observation made the treatment of disorders in this group, such as Duchene's muscular dystrophy and amyotrophic lateral sclerosis, with domiciliary NIV appealing. The physiological data investigating the modes of action has shown improvements in the ABG measurement and Epworth sleepiness score (ESS) comparing baseline to 3 months post NIV initiation.[123] The mechanism of action of NIV in this patient group appears to be via improvements in the hypercapnic ventilator response (HCVR) with Nickol *et al* demonstrating no significant change in pulmonary mechanics and an improvement in only one measure of respiratory

muscle strength following treatment with HMV for 3 months. In the same study, a dose response effect of nightly NIV usage was noted on $PaCO_2$, further supporting a true treatment effect.[123]

Initial data from retrospective and observational trials showed HMV is well tolerated and is associated with improved quality of life measures, fewer in-patient hospital days and high levels of survival.[124-126] The results of these studies must be interpreted carefully as there was no control group, historical data was used and patients who failed to tolerate NIV often proceeded to invasive ventilation. However, randomised controlled data has been produced in this area with Bourke *et al* studying 92 consecutive patients with amyotrophic lateral sclerosis and randomised 41, using a minimisation strategy to reduce potential confounders, to NIV or usual care when they reached a pre-set level of respiratory dysfunction.[127] Criteria for initiation of domiciliary NIV were symptomatic hypercapnia or orthopnoea with a MIP <60% predicted. Control (n=19) and NIV (n=22) patients were well matched at entry and all patients were followed up until 12 months or death. Results showed a significant survival advantage in the NIV arm over standard care (mean survival in days 219 vs 171; p=0.006) with improved HRQL indices as measured by the short form (SF)-36 questionnaire. The study had an *a priori* sub-analysis to examine if a survival advantage persisted in those patients with severe bulbar dysfunction. No benefit of NIV could be demonstrated with mean survival of 222 days in the NIV arm compared with 261 in the control group (p=0.92) in those patient with bulbar dysfunction. However, some quality of life improvement was shown in those patients with severe bulbar dysfunction randomised to NIV compared to controls. These data have been used to support the provision of domiciliary NIV for patients with neuromuscular disease, however, the optimum timing for initiation of ventilation is yet to be established. The majority of trials have used symptomatic daytime hypercapnia or evidence of profound respiratory muscle weakness as markers for initiation. Two studies have investigated the effects of earlier intervention in neuromuscular disease in order to better establish optimum indication for initiation of HMV. Raphaël *et al* recruited 70 patients with Duchene's muscular dystrophy free of daytime respiratory failure in a multicentre randomised controlled trial showing no difference in progression to

ventilatory failure.[128] However, of clinical concern was that there was an increased mortality in those patients randomised to the NIV arm. Interestingly, the patients were recruited without established respiratory failure and only a small minority satisfied criteria for domiciliary NIV by current clinical practice. A more structured approach was adopted by Ward *et al* by selecting 22 patients with daytime normocapnia but nocturnal hypoventilation.[20] Patients were randomised to either early (n=12) or standard (n=10) initiation of NIV. Within the 24 month follow-up of the trial all bar one patient from the delayed arm had required initiation of ventilation based on the development of diurnal hypercapnia, with 7 out of the 10 patients starting NIV in the first 12 months. The early initiation of therapy to reduce the risk of acute decompensation needs to be weighed against the inconvenience and any impact on HRQL of NIV. This trial used a combination of chest wall and neuromuscular disease but it may well be most pertinent in the management of neuromuscular diseases due to the progressive nature of the disease.

1.2.3: Evidence for domiciliary non-invasive ventilation in Chronic Obstructive Pulmonary Disease

The evidence for the use of NIV to support ventilatory failure in acute hypercapnic exacerbations of COPD is widely accepted and has demonstrated improved clinical outcomes compared to conventional management.[129-132] However, the use of domiciliary ventilation in COPD remains controversial.[133] A number of small physiological trials have demonstrated improvements in gas exchange,[134-136] health related quality of life,[136] pulmonary mechanics[134, 135, 137] and central respiratory drive.[137] Larger randomised controlled trials and subsequent meta-analyses have failed to translate these small studies into a clinical effect, with no significant improvements in clinical primary end points demonstrated.[93, 138, 139] The most recent and largest randomised clinical trial was reported by M^{c}Evoy and colleagues. The data demonstrated a small but significant survival advantage in stable hypercapnic COPD patients randomised to receive domiciliary NIV compared to standard care at a 2 year time point.[140] However, this survival advantage was only apparent in a *post hoc* adjusted analysis of the data and was subsequently lost using intention to treat analysis. Even when using the adjusted data, the outcomes of the Australian trial of non-

invasive Ventilation in Chronic Airway Limitation (AVCAL) study showed no early (<12 months) or long term (>3 years) benefit with the addition of HMV to standard care. Furthermore, randomisation to the NIV arm was associated with a poorer quality of life as measured by generic HRQL measures.

The main criticism of the negative studies in this area is that they have failed to adequately titrate the intervention (NIV) to the degree of physiological impairment (nocturnal hypoventilation). The mean pressure support provided in these studies is substantially below that which is used in clinical practice and in the earlier positive physiological studies. It is unsurprising that failure to adequately ventilate patients in chronic respiratory failure renders the intervention unsuccessful. Recent data from Dreher *et al* has supported this theory with a randomised crossover design trial employed to evaluate high and low intensity ventilatory strategies in chronic hypercapnic COPD.[141] During the high intensity treatment phase, patients had superior control of nocturnal hypoventilation than during the low intensity phase. Interestingly, the patients had better compliance with treatment during the high intensity treatment phase, in contrary to conventional expectation. Concerns regarding the effect of a high intensity approach on sleep quality have also been addressed, with no significant deterioration in sleep architecture seen in high versus low intensity NIV.[142] However, the data must be interpreted with caution in the most recent study as the study population were clinical patients who were all already established on high intensity NIV and thus may not reflect an unselected *de novo* population. The high intensity approach utilises both high inspiratory pressures and high back up rates; an approach that could be challenged when employed in COPD as it may fail to allow sufficient expiratory time to allow lung emptying, potentially exacerbating hyperinflation. A small randomised crossover trial performed by our group has investigated the contribution of changes in back up rate during high pressure HMV for hypercapnic COPD.[143] The study randomised patients with stable chronic respiratory failure secondary to COPD to either a high pressure and low back-up rate ventilatory strategy (PSV) or a high pressure and high back-up rate ventilatory strategy (PCV) for a 6 week period followed by crossing over to the alternate arm for another 6 weeks. 12 patients were randomised with 7 completing the whole protocol.

Both PSV and PCV produced a similar degree of control nocturnal hypoventilation (PSV overnight $tcCO_2$ 6.5 ± 1.2 kPa vs PCV overnight $tcCO_2$ 6.5 ± 1.3, p=0.985) and daytime gas exchange (PSV $PaCO_2$ 7.2 ± 0.8 kPa vs PCV $PaCO_2$ 7.0 ± 0.8, p=0.190). There was also similar degrees of objective (PSV sleep efficiency 77 ± 12% vs PCV sleep efficiency 73 ± 18, p=0.484) and subjective (PSV sleep comfort VAS 57 ± 29 vs PCV sleep comfort VAS 58 ± 29, p=0.944) sleep quality. These data suggest that the high pressure is the important feature of the high intensity approach and that there is no additional clinical or physiological benefit from adding a high back-up rate. The equivocal nature of the evidence has led to substantial variation in practice across Europe in this area.[144]

In addition to the failure of earlier trials to maximise the therapeutic benefit of HMV with high pressure setup, these trials have also been criticised as they have only recruited the most stable of hypercapnic COPD patients.[93, 140] There has been increasing interest in the use of HMV to target those patients with repeated decompensated exacerbations requiring acute NIV.[145] Patients who have required acute NIV for a decompensated hypercapnic exacerbation of COPD have a poor prognosis with high levels of morbidity and mortality.[146-148] These historic outcomes have improved little with recent unselected data demonstrating a 1 year mortality of over 50% following the first episode of decompensated respiratory failure with the majority of deaths occurring in the 3 months following hospital discharge.[149] A pilot randomised controlled trial has been completed that randomised patients to either HMV or CPAP following an acute exacerbation requiring NIV.[150] Whilst the trial showed a significant reduction in episodes of recurrent hypercapnic exacerbations requiring NIV at 1 year (NIV group 39%, CPAP group 60%, p=0.04) there were no between group differences in hospital admissions due to exacerbations of COPD (p=0.48), mortality (p=0.86) or $PaCO_2$ (p=0.49). The specific end-point used in this study means limited conclusions can be drawn on any possible clinical benefit. Despite the limited evidence in this area the poor prognosis has led some centres to routinely offer HMV to patients following an inpatient episode requiring acute NIV. This cohort of patients has been the subject of investigation of the clinical and physiological effects of subsequent withdrawal

of NIV therapy by Funk *et al*.[151] Patients were initiated on HMV following an acute hypercapnic exacerbation and following a 6 month period of stability on HMV were subsequently randomised to continuation of HMV or HMV withdrawal. The primary outcome was a clinical deterioration; pre-specified as need for escalation of mechanical ventilation, 10% rise in $PaCO_2$ or intractable dyspnoea necessitating NIV for relief. The final criterion was patient rather than physician judged. Patients randomised to the withdrawal group were more likely to meet the primary outcome than those who continued to receive HMV (continuation group 15%, withdrawal group 77%, p=0.005). However, if this was restricted to the single criterion that applied to both groups, a need for escalation of mechanical ventilation, there was no between group difference (continuation group 15%, withdrawal group 23%, p value not reported). There were no between group differences in either antibiotic usage (p=0.35) or incidence of oral steroid therapy (p=0.59) during the 1 year study period. The use of both subjective and arbitrary criteria to comprise the primary outcome limits the interpretation that can be made of the data.

1.2.4: Evidence for domiciliary non-invasive ventilation in obesity hypoventilation syndrome

The epidemic of obesity in the western world has led to an increase in a range of obesity related complications including respiratory problems and sleep disordered breathing.[152] Whilst OSA is relatively well known by both medical and lay people, OHS, despite its high mortality, remains poorly understood and under diagnosed.[153] OHS was originally described in a case report by Auchincloss *et al* in 1955[154] although the commonly used term Pickwickian syndrome was not coined until the following year when the condition was linked to hypersomnolence.[155] The syndrome is now commonly recognised as the presence of obesity (BMI > 30 kgm^{-2}), daytime respiratory failure ($PaCO_2$ > 6 kPa) and sleep disordered breathing in the absence of another identifiable cause of hypoventilation.[156, 157] While the true population prevalence is unknown it is increasingly common with increasing BMI[158, 159] and is known to be highly prevalent in acute medical attendees[153] and patients attending sleep disorder services.[158] Patients with OHS have a poorer prognosis than similarly obese eucapnic patients[153] but there has yet to be a randomised controlled trial

of NIV compared to sham ventilation or no treatment powered to examine long term outcomes. Current evidence for treatment is based on a collection of uncontrolled, non-randomised or short trials involving either CPAP or bi-level NIV. These studies demonstrate short[234] and long[164] term efficacy of therapy with improvements in daytime somnolence,[160] health related quality of life[92] and gas exchange.[161] The only randomised controlled comparing domiciliary NIV to a control group was recently published by Borel *et al*.[162] In this study lifestyle counselling was used as the control due to the difficulties of sham NIV. Patients receiving domiciliary NIV had a greater improvement in $PaCO_2$ (mean difference -0.5 kPa, 95%CI -0.8 to -0.1, p=0.015), and sleep architecture, although surprisingly no significant between group difference in daytime somnolence was demonstrated (Control group ΔESS -2.1, 95%CI -4.5 to 0.4; NIV group ΔESS -3.4, 95%CI -6.0 to -0.8; between group p=ns). Whilst the need for treatment in this group to improve symptoms and clinical outcomes is generally accepted the optimum ventilatory strategy is yet to be clearly elucidated. There are few trials directly comparing ventilatory modes in OHS with Piper *et al* comparing CPAP to bi-level NIV and Storre *et al* investigating the addition of volume targeted pressure support ventilation, average volume assured pressure support (AVAPS), to standard NIV. In the latter study the addition of AVAPS was associated with improved nocturnal ventilatory control and equivalent improvements in gas exchange and HRQL.[92] However, concern has been raised regarding the potential for the variable pressure support to contribute to increased sleep disruption.[163] Piper and colleagues performed a randomised controlled trial comparing CPAP therapy and bilevel NIV in obese patients with chronic respiratory failure who did not exhibit significant nocturnal hypoventilation during CPAP therapy.[160] The study showed no significant difference in either gas exchange or HRQL following 3 months of therapy. Due to the highly selected cohort of patients enrolled in this trial, the applicability of these findings to clinical practice remains unclear and concern is raised when examining the findings of the study by Banerjee *et al*, which demonstrated continued severe hypoxaemia in patients with OHS compared to matched eucapnic OSA patients when managed with CPAP alone.[164] Despite the lack of randomised controlled trials there is much evidence to support a survival advantage in patients with OHS treated with long term NIV.[165, 166] These data

raise ethical issues and the controlled trials in the future are likely to require a delayed treatment arm and therefore the length of the trial will be limited to three months which will adversely impact on our understanding of the long-term outcome.

CHAPTER 2: HYPOTHESES

2.1: Translation of Evidence from Bench to Bedside

The current evidence for advanced physiological measurement and monitoring techniques and domiciliary NIV in patients with respiratory failure is variable across different acute and long term patient groups and this has led to different challenges in each setting.

Whilst lacking a prospective randomised controlled trial to support long term benefits of domiciliary NIV in OHS, there is clear consensus that symptomatic benefits of treatment, and probable mortality benefits, renders this unethical. However, there is uncertainty as to the optimum ventilatory approach in this syndrome, leading to a wide variation in practice; from the use of single level CPAP, through to the fixed bilevel devices, to the more advanced ventilatory modes. The use of a mode that can adapt to changing physiological loads during sleep may have significant benefit.

Employing advanced physiological monitoring techniques in patients during an acute respiratory deterioration is challenging, but currently we have limited approaches to assessing treatment failure and quantifying the risk of readmission to hospital. Therefore, utilising the physiological measure of neural respiratory drive as a clinical tool could provide greater understanding of the changes in physiology that occur during an exacerbation of COPD as well as risk stratifying these patients during their admission.

The challenge, in the context of chronic respiratory failure secondary to COPD is different with the equivocal evidence limiting the current clinical use of the intervention. However, the intuitive benefits of domiciliary ventilation raise the potential for successful application if the correct patients and correct ventilatory strategy can be selected. A more detailed knowledge of the pathophysiology of chronic respiratory failure, as well as the time course and effect of acute exacerbation on the chronic condition, is required to optimise the approach to non-invasive ventilation set up in this group.

To address these three areas, three physiological trials were performed which were based on the pathophysiological mechanisms involved in each specific situation, namely an imbalance between respiratory muscle load, capacity and drive; these are detailed below.

2.2: Physiological Trial 1: Volume Targeted Pressure Support Ventilation Compared to Fixed Level Nurse led Protocolised Pressure Support in Obese Patients with Chronic Respiratory Failure

The pathophysiological mechanism of chronic respiratory failure in OHS is yet to be fully elucidated, however, an imbalance between respiratory muscle load, capacity and neural respiratory drive is key.

2.2.1: Respiratory drive

Patients with OHS have been shown to have decreased ventilatory responses to carbon dioxide compared to eucapnic obese and patients with simple OSA.[167] The level of NRD, as indicated by EMG_{di}, are increased in simple obesity but in OHS patients there is failure for this to be translated to an improved response to CO_2.[54, 168] Despite the presence of diurnal hypercapnia, patients with OHS can voluntarily hyperventilate in order to become eucapnia implying the ventilatory constraints alone are not responsible for this phenomenon.[169] The presence of sleep disorder breathing promotes sleep disruption[170] and this itself can impair central respiratory drive by reducing HCVR.[171-173] The use of NIV in OHS promotes sleep consolidation and may therefore act to improve central respiratory drive.[162, 164] Uncontrolled studies have found that the degree of REM hypoventilation correlates to the daytime HCVR and that it can be shown that the HCVR improves following treatment with NIV.[174, 175] In contrast, the only randomised controlled trial performed failed to demonstrate a treatment effect on central respiratory drive, as measured by HCVR[162], although this may be explained by the selection methods used. Patients were recruited from sleep centres and advertisements and enrolled if hypercapnic. However, baseline values were taken 1-2 weeks later when a proportion of patients were no-longer hypercapnic (mean $PaCO_2$ control group

6.0 ± 0.4 kPa, NIV group 6.4 ± 0.6 kPa) and therefore did not strictly meet the criteria for a diagnosis of OHS at this point. If following the successful treatment of OHS with NIV, therapy is withdrawn then the HCVR is attenuated.[176] Sleep disordered breathing in OHS can be the result of OSA, pure nocturnal hypoventilation or a combination of the 2 contributing to nocturnal hypoxia.[177] The presence of prolonged hypoxia occurring during nocturnal hypoventilation itself may further exacerbate the reduction in central drive. Healthy volunteers exposed to prolonged mild hypoxia during sleep had significantly dampened responses to resistive loads during sleep.[178] This impaired ventilatory response post apnoea offers another potential avenue for the development of diurnal respiratory failure in OHS.

2.2.2: Respiratory load

Obesity acts to impair pulmonary mechanics in a number of ways with abdominal and thoracic adiposity directly increases the load, as measured by pulmonary compliance, on the respiratory system.[179] The generation of intrinsic PEEP when in the supine posture, as is usual for sleep, creates a threshold load in obesity.[180] Respiratory mechanics are further impaired by the reduction in lung volumes that are associated with moderate and severe obesity.[181] These changes in lung volumes adversely affect pulmonary mechanics by increasing airway resistance[182] as well as contributing to reducing pulmonary compliance.[183] Upper airways resistance can also be shown to be higher in patients with OHS compared to eucapnic OSA patients.[184] These factors all act to increases the work of breathing which appears to be more pronounced in OHS than in similarly obese eucapnic patients.[185, 186] Furthermore, the reduction in FRC contributes to ventilation-perfusion mismatching and the adoption of a small tidal volume and a rapid respiratory rate.[187] The normalisation of gas exchange that follows significant weight loss indicates that the reduction in this pathological level of load is important in disease resolution.[188]

2.2.3: Respiratory muscle capacity

Inspiratory muscle strength and endurance is reported as normal[189] or slightly reduced[190] in simple obesity but markedly impaired in OHS.[191] This impairment is exaggerated by the supine posture[192] and thus more prominent during sleep.

Maximum voluntary ventilation is impaired in OHS compared to eucapnic obese and this correlates with degree of hypercapnia.[193] This loss of respiratory muscle capacity may be related to the hypoxia and hypercapnia that are hallmark features of OHS.[194]

2.2.4: Summary

The interaction between obesity and sleep disordered breathing further alters the load-capacity-drive relationship of the respiratory system.[167, 169, 185] This relationship differs during changes in body position and sleep stage.[54, 195] The standard treatment of OHS with fixed CPAP or bi-level NIV does not alter to maintain ventilation during these changes. Newer ventilatory modes have been developed that estimate the expiratory tidal volume during ventilation and respond by altering the inspiratory pressure provided in order to optimise respiratory support. Storre *et al* demonstrated that the use of volume targeted pressure support mode provided greater control of sleep disordered breathing than fixed bi-level pressure support ventilation.[92] However, concerns have been raised that the variable pressure support may contribute to greater sleep disruption.[163] These two studies were not designed to minimise the differences between the two ventilatory modes and significant differences in the setup strategies led to significantly higher delivered pressure support in the volume targeted pressure support ventilation group. It is perhaps expected that these higher levels of pressure support provided greater control of nocturnal hypoventilation but at the cost of increased sleep disruption.

The trial reported in this thesis prospectively examined the advantages of the use of the volume targeted pressure support mode in the treatment of OHS using a single blind randomised controlled trial design with aim of exploring the following hypotheses:

1. Superior control of nocturnal hypoventilation will lead to greater improvements in daytime gas exchange.
2. Volume targeted pressure support ventilation will improve ventilator comfort and enhance compliance.

3. Improved control of nocturnal hypoventilation will provide greater improvements in daytime somnolence and health related quality of life.

4. Improvements in daytime somnolence will be associated with an increase in daytime physical activity and weight loss.

2.3: Physiological Trial 2: Advanced Physiological Monitoring in Patients During Hospital Admissions for Acute Exacerbation of Chronic Obstructive Pulmonary Disease

Acute exacerbations of chronic obstructive pulmonary disease are a major economic burden to healthcare systems.[196, 197] In addition, exacerbations have a significant impact on HRQL with admission avoidance and reduced length of hospital admission becoming national targets.[198] Recently, healthcare systems, including the National Health Service, have focused on providing enhanced community care to facilitate early discharge.[199-201] Acute care organisations have incorporated early warning scores, integrating basic cardiorespiratory and other physiological variables into a composite score, as predictors of clinical deterioration. However, the clinical usefulness of such scoring systems remains controversial.[202-206] All these monitoring systems require accurate characterisation of disease severity and response to treatment to identify patients that are either deteriorating or only slowly improving to allocate patients to higher levels of clinical care. There are few physiological biomarkers available that have sufficient sensitivity and specificity to identify patients failing to respond to treatment in acute exacerbations of COPD.[207] Whilst the majority of cases of respiratory failure due to acute exacerbations of COPD are present at admission to hospital a significant minority develop decompensated respiratory failure during the ward stay.[208] The utilisation of neural respiratory drive to measure the clinical response to treatment in acute exacerbations of COPD and identify this deterioration has not previously been reported.

2.3.1: Respiratory drive

Neural respiratory drive, which reflects the balance between respiratory muscle load and capacity, measured using the EMG_{di}, has been shown to relate to disease severity in stable COPD.[53] As expected, this technique has been

limited in its application, particularly in the acute setting, as it requires the placement of an oesophageal electrode to measure EMG_{di}. Clinical interest has therefore been directed towards measuring the EMG of the parasternal intercostal muscles, which can be studied in a less invasive manner.[209] The chest wall respiratory muscles have increased importance in patients with advanced COPD as progressive hyperinflation impacts adversely on diaphragm positioning and efficiency,[80, 210] which results in a compensatory increase in chest wall and accessory respiratory muscle activity.[211, 212] In particular, the uppermost parasternal intercostal muscles have been shown to be important inspiratory muscles.[213-215] Furthermore, these parasternal muscles have minimal post-inspiratory activity[216] with the 2nd intercostal space (ICS) parasternal muscle demonstrating similar activity to the diaphragm.[217] During increasing hyperinflation, as observed during an acute exacerbation of COPD, the resting length of the parasternals is less affected than the diaphragm, such that the parasternals make a greater contribution to inspiratory pressure generation.[218] This increase in parasternal activity is also associated with higher levels of dyspnoea.[219] Previous work has also demonstrated that EMG_{para}, recorded from surface electrodes, has a direct relationship with respiratory muscle load.[220] Furthermore, it is a measurement that is responsive to clinical changes during exacerbations in both childhood asthma[221, 222] and cystic fibrosis[223] following treatment.

2.3.2: Respiratory load

Acute exacerbations of COPD produce an acute on chronic increase in the load on the respiratory system.[224] The changes in load are mediated via changes to both inspiratory resistance and dynamic chest wall elastance as well as threshold load exerted by intrinsic PEEP.[225] This acute increase in load on the respiratory system causes a significant increase in the work of breathing with transdiaphragmatic pressure changes in patients with acute exacerbations of COPD being double that of stable counterparts.[226, 227] These effects can be further exacerbated by dynamic hyperinflation resulting from severe flow limitation impairing expiratory flow time.[228]

2.3.3: Respiratory muscle capacity

The volitional and non-volitional pressure generating capacity of the inspiratory muscles is reduced in COPD.[229] However, hyperinflation produces a mechanical disadvantage for the diaphragm negatively affecting its pressure generating capacity.[230] Therefore, when lung volumes are taken into account the pressures generated by COPD patients are similar to those of healthy subjects.[57] The metabolic properties of the respiratory muscles in patients with COPD, in particular the diaphragm, have been demonstrated *in vitro*[231] to have a favourable shift to fatigue resistant fibres,[232] suggesting only a limited role of respiratory muscle weakness in the development of respiratory failure in COPD.

2.3.4: Summary

Complex physiological assessment of the respiratory system during acute exacerbations of COPD is unlikely to become a clinical tool due to the necessary expertise needed and the invasive nature of the procedures. The use of 2nd intercostal space parasternal muscle EMG (EMG_{para}) to monitor respiratory-drive during exacerbations offers an opportunity to detect early treatment failure and the need for ventilatory support.

We designed a prospective observational study measuring NRD using EMG_{para} to investigate the sensitivity and specificity for detecting clinical deterioration during an acute exacerbation. The study was designed to answer the following hypotheses:

1. NRD, as measured by EMG_{para}, is reproducible in stable COPD.
2. Changes in NRD precede standard measures of clinical deterioration during acute exacerbations of COPD.
3. Failure of NRD to fall during treatment of an acute exacerbation of COPD prior to hospital discharge predicts readmission risk.

2.4: Physiological Trial 3: Physiological Effects of Home Mechanical Ventilation Compared to Home Oxygen Therapy in Patients with Persistent Hypercapnic Following Acute Exacerbations of Chronic Obstructive Pulmonary Disease

The equivocal data concerning the use of domiciliary NIV in COPD are principally attributable to poor trial design. There has been a failure to maximise the chances of a successful trial outcome by ensuring that the trial selects the highest risk patients and optimises the intervention. Patients presenting with acute decompensated hypercapnia have a poor prognosis with high rates of readmission and death[146, 147] making them ideal candidates for a therapeutic intervention. The majority of published trials titrated inspiratory pressure to comfort or subjective relief of dyspnoea during wakefulness, providing less than optimal levels of ventilatory support.[93, 138, 140] None of these trials showed significant improvements in gas exchange in the intervention group, implying failure to adequately augment ventilation. It is unsurprising therefore that the trials did not show significant clinical advantages in the therapeutic group as in effect they were receiving sub-therapeutic or sham intervention. Trials involving higher levels of pressure support and reporting significant improvements in gas exchange have involved high inspiratory pressures.[135, 136]

As already alluded to earlier in this chapter much of the equivocal data from large clinical trials of HMV in COPD have been criticised due to their failure to correct nocturnal hypoventilation. The advent of high intensity ventilation for COPD has been supported by data that has been shown it to better control nocturnal hypoventilation than lower intensity non-invasive ventilation.[141] Although the effects on sleep quality are unclear the data suggests that the control of hyponocturnal ventilation is likely to have an equivocal or even beneficial effect on sleep quality.[136, 142] The previous work by both Dreher *et al* and Meecham-Jones *et al* used overnight in-hospital polysomnography to compare the disruptive effects of nocturnal NIV on sleep quality.[136, 142] Whilst this allows detailed exploration of sleep architecture it requires extensive monitoring for a single night within hospital. Despite the inability of actigraphy to record detailed sleep staging it has the advantage of allowing the monitoring of patients for prolonged periods in their own home, which better reflects the patients usual sleep pattern and sleep quality. Three main hypotheses have been suggested to explain the improvement in daytime gas exchange of HMV in COPD patients with chronic hypercapnic respiratory failure:

1. Resetting central respiratory drive.
2. Improving pulmonary mechanics.
3. Resting fatigued respiratory muscles.

The relative merits of each hypothesis are discussed below.

2.4.1: Respiratory drive

Due to the increased respiratory muscle load, patients with COPD have an increased level of NRD as measured by EMG_{di}, HCVR and $P_{0.1}$.[53, 233] However, COPD patients with chronic hypercapnia fail to increase NRD levels in response to further carbon dioxide stimulus.[233] This reduction in central chemosensitivity is considered to be a major cause of persistent hypercapnia and it can be modified by even short periods of daytime NIV[137] and it is inversely correlated with changes in daytime $PaCO_2$, supportive of a mechanistic role in mediating the change.[134] The measurement of central respiratory drive can be challenging and two main methods have been used: the hypercapnic ventilator response (HCVR)[234] test and measurement of $P_{0.1}$.[60] Both tests have been shown to improve following HMV in hypercapnic COPD[134, 137, 235, 236] with the former demonstrated to be reliable and reproducible in severe COPD[237] whilst the performance of the latter measurement in this patient group has been variable.[238] However, the reliability and reproducibility of HCVR has been questioned as ventilatory response is influenced by mechanical factors, such as airflow limitation and changes in lung volume, which are altered in COPD as ventilation increases and lung empting is incomplete.[239] Researchers often corrected the HCVR to either forced expiratory volume in one second (FEV_1)[137] or maximum voluntary ventilation (MVV)[240] in an attempt to account for the mechanical limitations of the test and variations in body size. The use of changes in NRD, measured using diaphragm and parasternal EMG, during hypercapnic challenge testing may better represent central drive than the use of minute ventilation. Blunting of the respiratory drive leads to nocturnal hypoventilation and significant sleep disordered breathing.[241] Patients with both COPD and significant sleep disordered breathing have a poor prognosis if left untreated and outcomes are improved by control of the sleep disordered breathing.[242] Variation in neural respiratory drive appears an important element of exercise restriction in severe COPD and its modification offers the potential to

improve exercise capacity and thus physical activity.[243] Indeed changes in dyspnoea following pulmonary rehabilitation programmes have been shown to correlate with changes in objectively measured physical activity.[244]

2.4.2: Respiratory load

COPD is characterised by significant increases in the load on the respiratory system. A major contributor to this is a modification in the operating lung volumes with static hyperinflation which places the respiratory system on a less efficient part of the pressure-volume curve. The airflow limitation that is the hallmark of COPD can further exacerbate this problem, especially as during exercise minute ventilation increases, which leads to dynamic hyperinflation.[228] The degree of hyperinflation as measured by the inspiratory capacity/total lung capacity (IC/TLC) ratio provides a global indication of respiratory load and, more importantly, it has been shown to have prognostic value in stable COPD.[245] Improvements in the degree of hyperinflation following treatment with NIV have been demonstrated with the degree of improvement correlating with improvements in gas exchange.[134, 137] Long term use of NIV has also been shown to reduce load by improving dynamic lung compliance (C_{dyn}),[236] dynamic intrinsic positive end expiratory pressure ($_{dyn}PEEP_i$),[236] airflow obstruction,[135] and resting respiratory pattern.[235, 236] However, the changes observed have been inconsistent across the studies. The mechanical constraints imposed by both static and exercise induced dynamic hyperinflation appear to be the most significant limiting factor in endurance exercise capacity in COPD.[113] Thus, improvements in this area offer the opportunity to release this critical constraint allowing improved exercise performance.

2.4.3: Respiratory muscle capacity

Initial theories regarding the mechanism of action of NIV in COPD revolved around the idea of 'resting' the fatigued respiratory muscles. More recent work has indicated that the respiratory muscles in COPD are at a cellular level more efficient than healthy controls[231] and this is thought to be due to a fibre shift from type 2 fatigue sensitive glycolytic fibres to type 1 fatigue resistant oxidative fibres within the muscle.[232] Furthermore, there has been a failure to demonstrate diaphragm fatigue *in vivo* in COPD patients,[246] even in those patients requiring mechanical ventilation.[247] All the studies to date have not

shown any clinically meaningful changes in respiratory muscle function following treatment with NIV in severe hypercapnic COPD.[93, 137, 138, 248, 249]

2.4.4: Summary

Whilst much data has been published reporting the physiological changes occurring following the initiation of domiciliary NIV, interpretation of the data has been limited by the lack of a comparative control group in the studies.[134, 137] Three studies have attempted to use control groups to examine the physiological changes caused by HMV. However, these studies have been limited by the use of either a non-randomised design[235] or application of NIV in a hospital rather than the domiciliary setting,[135, 236] as well as of being of relatively short duration. These methodological flaws limit the conclusions that can be drawn from these physiological data. The lack of a clear clinical response to HMV in COPD provides a robust case for a physiological randomised controlled trial.

A randomised controlled trial comparing standard care (home oxygen therapy) to standard care with the addition of domiciliary NIV will allow the following hypotheses to be tested:

1. The principal physiological mechanism of action of domiciliary NIV in hypercapnic COPD is a combination of improved central chemosensitvity and enhanced pulmonary mechanics.

2. Changes in central respiratory drive using NRD, measures such as EMG_{di} and EMG_{para}, provides greater physiological understanding than traditional measures of ventilation output (V_e).

3. Sleep quality is similar in patients treated with home oxygen therapy and domiciliary NIV.

4. Daytime physical activity is enhanced in patients treated with domiciliary NIV compared patients treated with home oxygen therapy.

3.1: Ethical Approval

All of the studies described had prior ethical approval from either King's College Hospital or St Thomas' Hospital ethics committee:

- Study 1 – 07/H0804/140
- Study 2 – 05/Q0703/82
- Study 3 – 09/H0802/2

3.2: Patient Recruitment

3.2.1: Study 1

Patients referred to the Lane Fox Respiratory Unit, Guy's and St Thomas' Hospital and the Sleep and Ventilation Unit, Royal Brompton Hospital with stable OHS or transferred following acute decompensated respiratory failure secondary to OHS were screened for study inclusion.

Study inclusion criteria were:

- Obesity with a BMI >40 kg/m^2
- Daytime stable respiratory failure with $PaCO_2$ >6 kPa and pH >7.35
- Absence of another identifiable cause of hypoventilation
- Ratio of FEV_1 to FVC >0.70 and FVC <70% predicted

Exclusion criterion was*:*

- An inability to provide written informed consent

3.2.2: Study 2

Stable COPD patients were recruited from the pulmonary rehabilitation programme at St Thomas' Hospital. Patients admitted to a medical ward via the accident and emergency department at St Thomas' Hospital with a primary diagnosis of an acute exacerbation of COPD were offered enrolment in the study.

3.2.3: Study 3

Patients referred to the Lane Fox Respiratory Unit, St Thomas' Hospital and the Sleep & Ventilation Unit, Royal Brompton Hospital with persistent hypercapnia following a recent admission with decompensated acute on chronic respiratory failure secondary to an acute exacerbation of COPD were screened for suitability for participation. In addition, patients recruited from Aintree University Hospital and Leeds University Hospital were offered participation in the actigraphy assessed sleep quality sub-study.

Inclusion criteria were:

- An inpatient admission with an acute hypercapnic exacerbation of COPD
- A greater than 20 pack year smoking history
- FEV_1 of less than 50% predicted
- FEV_1/FVC less than 60%
- At least 2 weeks following resolution of acute hypercapnic acidosis ($PaCO_2$ >7 kPa, pH >7.3)
- Chronic hypoxia (P_aO_2 <7.3 kPa or <8 kPa with secondary polycythaemia, pulmonary hypertension, peripheral oedema or significant nocturnal hypoxia (SpO_2 <90% for >30% sleep time)

Exclusion criteria were:

- Inability to wean off NIV prior to discharge/transfer (persistent hypercapnic respiratory failure with pH <7.30 despite adequate NIV)
- Patient requiring daytime NIV or >6 hours of nocturnal NIV
- Development of worsening hypercapnic respiratory failure with acidosis during initiation of oxygen therapy (ABG – pH <7.30 taken 2-4 hours after waking)
- Primary diagnosis of restrictive lung disease causing hypercapnia
- Significant symptomatic OSA contributing to patient morbidity
- Assessment more than 4 weeks from resolution of index exacerbation
- BMI >35 kgm^{-2}
- Need for invasive mechanical ventilation during acute admission
- Unable to tolerate NIV (if given) during acute illness

- Unstable coronary artery syndrome
- Renal replacement therapy
- Inability to consent/comply with trial protocol (as determined by site PI)
- Aged <18 years
- Pregnancy

3.3: Anthropometrics

3.3.1: Basic anthropometrics

Height and weight were measured in patients wearing light clothing and without shoes. Waist measurement was taken at the midpoint between the lower costal margin and the iliac crest. Hip measurement was made at the point of largest lateral protrusion of the hips.

3.3.2: Measurement of fat free mass (FFM)

Single frequency bioelectrical impedance (Bodystat 1500, Bodystat, Douglas, UK) was used to calculate participants' FFM. The technique involves passage of a small current at 50Hz between surface electrodes placed on the extremities. The unit calculates the voltage drop between the electrodes and thus total body impedance. The test assumes a two compartment model with adipose tissue containing little or no water and electrolytes and therefore being of high electrical impedance and FFM having a high water and electrolyte content and thus low electrical impedance. Predictive equations can then be used that incorporate height, weight, age and gender in order to calculate FFM from the measured impedance value. Generic and disease specific regression equations exist to maximise the accuracy of the results with the technique validated against other methods of measuring body composition such as dual energy x-ray absorptiometry (DEXA).[250, 251]

3.4: Health Related Quality of Life

A range of generic and population specific validated questionnaires were used to assess health related quality of life in the studies.

3.4.1: St George's respiratory questionnaire (SGRQ)

Originally validated in 1992, in patients with both fixed and reversible airflow limitation, the questionnaire is self-administered and comprises of 72 questions.[87] Once completed the questionnaire provides a total and 3 sub-domain scores relating to symptoms, impact (on daily life) and activity. It has been shown to be reproducible and sensitive to changes in disease state.[252] The version of the SGRQ used during this work is provided at the end of this work (Appendix A: SGRQ).

3.4.2: Severe respiratory insufficiency (SRI) questionnaire

Patients with respiratory failure receiving domiciliary NIV consist of a number of different diagnostic categories but suffer with a range of problems related to both the underlying disease process and the resultant sleep disordered breathing. The SRI questionnaire comprises of 49 questions producing a summary and 7 sub-domain scores. The questionnaire has been validated in the general HMV population and specifically in COPD patients receiving HMV and has been shown to be reproducible and correlates to changes in generic measures of HRQL.[89, 90] The questionnaire was originally formulated in German but has also been validated in Spanish and English.[253, 254] The English version of the SRI is provided in the appendix (Appendix B: SRI questionnaire).

3.4.3: Epworth sleepiness score (ESS)

Daytime somnolence can be a feature of all forms of sleep disordered breathing and it is distinct from either fatigue or tiredness. The Epworth sleepiness questionnaire was validated in a sleep disorder setting to differentiate the pathologically sleepy states that occur in OSA, narcolepsy and idiopathic hypersomnolence from simple snoring or a healthy control population, with values correlating to sleep latency during polysomnography and multiple sleep latency testing.[255] The ESS has subsequently been used to monitor response to treatment in forms of respiratory failure and sleep disordered breathing.[123, 256] A reproduction of the ESS is provided in the appendix (Appendix C: ESS).

3.4.4: Chronic respiratory disease questionnaire (CRQ)

The CRQ was developed for use in clinical trials. This was because it was acknowledged that a disparity existed between pulmonary function testing,

physical activity, dyspnoea and functional state in COPD. The CRQ was initially developed as an interviewer administered questionnaire and it was subsequently modified to incorporate an individualised dyspnoea component and be self-administered.[88, 257] As with other HRQL measures in COPD it has been demonstrated to be reproducible and responsive to clinical change occurring following optimisation of medical therapy or pulmonary rehabilitation.[88] The questionnaire provides scores in 4 domains relating to dyspnoea, emotional function, fatigue and mastery (patients control over illness). The self-administered individualised CRQ is provided in the appendix at the end of this document (Appendix D: CRQ-SAI).

3.5: Exercise Capacity and Physical Activity

Physical activity is both a patient centred outcome and implicated in the disease process itself in COPD. Exercise performance is an important prognostic factor in COPD and in the HMV population.[104, 258]

3.5.1: Incremental shuttle walk test

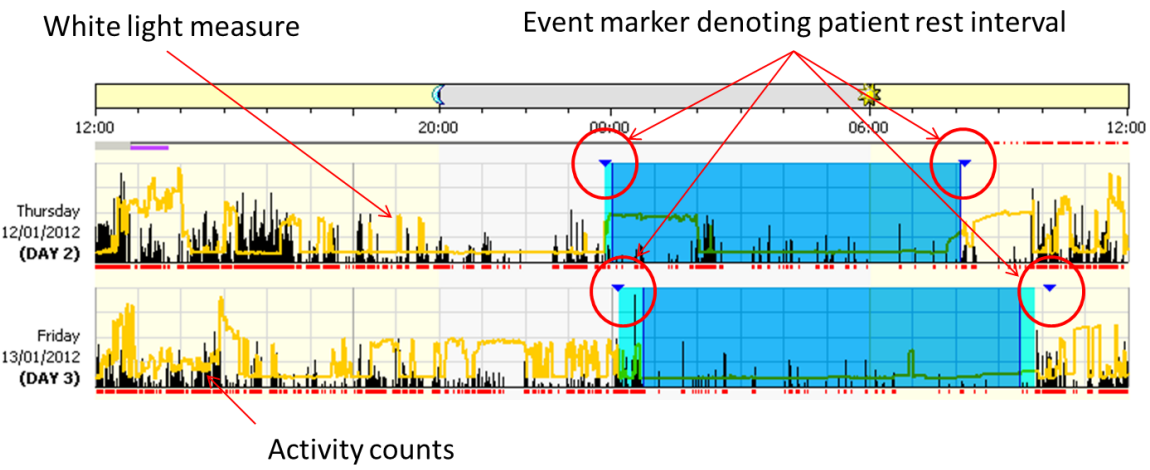
The ISWT provides a symptom limited test of maximum exercise performance that correlates with 6 minute walking test time.[95] The test is performed on a 10m course and is externally paced by using a beep system which starts with long pauses and steadily increasing in frequency over the duration of the test. The test is continued until the patient is unable to complete the course at the necessary pace or is no longer able to continue. Performance on the ISWT correlates strongly with maximum oxygen consumption[259] and has been shown to correlate with significant outcomes such as mortality in COPD.[260] Data indicates that the minimum clinically important difference is 47.5m.[261]

3.5.2: Actigraphy

Physical activity can be assessed by means of wrist worn actigraphs. The Actiwatch 64 (Philips-Respironics, Murrysville, PA, US) and Actiwatch Spectrum (Philips-Respironics, Murrysville, PA, US) consist of an accelerometer and event button. They produce an activity count that is proportional to the speed and duration of movement during 1 minute epochs. They allow for the objective assessment of physical activity in an unobtrusive way and have been used to

monitor physical activity in obesity[262] and COPD.[263] Watches were fitted on the non-dominant wrist in COPD and dominant wrist in obesity and worn for 14 days, except for short periods for personal hygiene. The patients completed a sleep hygiene diary (Appendix E: sleep hygiene diary) during this time and returned it with the watch. Following the assessment period data were downloaded via Actiware 5 (Philips-Respironics, Murrysville, PA, US) allowing detailed analysis of patterns of physical activity. Using a combination of sleep diary, event marker and light sensor readings rest periods were set on the actigram as shown in Figure 8.

Figure 8: Example actigram with light, activity and event markers used to place rest intervals



Physical activity was calculated for the time in between the daily major rest period, termed 'daytime', for a seven day period. The following data was produced:

- Mean activity - mean daytime activity counts per 1 minute epoch
- Peak activity - mean peak 1 minute epoch daytime activity count
- Total mobile time - mean daytime total number of 1 minute epochs with activity (minutes and percentage daytime)
- Total immobile time - mean daytime total number of 1 minute epochs with no activity (minutes and percentage daytime)

3.6: Pulmonary Mechanics

3.6.1: Pulmonary function testing

Testing was performed in the pulmonary function laboratories at St Thomas' Hospital and the Royal Brompton Hospital and conducted by departmental staff. Spirometric, plethysmographic, gas transfer and lung volumes were obtained using standardised testing.[264] Predictive values were obtained using European Respiratory Society standards.[265]

3.6.2: Advanced pulmonary mechanics measurements

The assessment of detailed pulmonary mechanics requires the measurement of flow and of pressure changes across the respiratory system. The process by which these are obtained is detailed below. Following signal acquisition analogue to digital conversion was performed by a Powerlab device (ADInstuments, Chalgrove, UK). Once digitised signals could be viewed and manipulated on a personal computer using a commercial software package (Labchart v7.2, ADInstuments, Chalgrove, UK).

Measurement of respiratory pressures

Differential pressure transducers (MP 45, Validyne, Northridge, CA, US) attached via amplifiers to the Powerlab system allowed recording of the desired pressures. The transducers were individually connected via low bore non-compliant tubing to a nasal bung, oesophageal balloon and gastric balloon. This allowed simultaneous measures to be taken across the respiratory system. The pressure transducers were calibrated against a digital manometer (Bio-Tek Instruments, Winooski, VT, US) using a two-point calibration test. The system was calibrated to atmospheric pressure and then to a second pressure (nasal and oesophageal transducer -150cmH_2O, gastric transducer +150cmH_2O) generated via a 50ml syringe and 3 way tap connected to the pressure transducer. Linearity was tested to ensure readings were within 1% across the range -150 to 150 cmH_2O. Calibration was performed prior to each patient testing.

Oesophageal and gastric balloon positioning

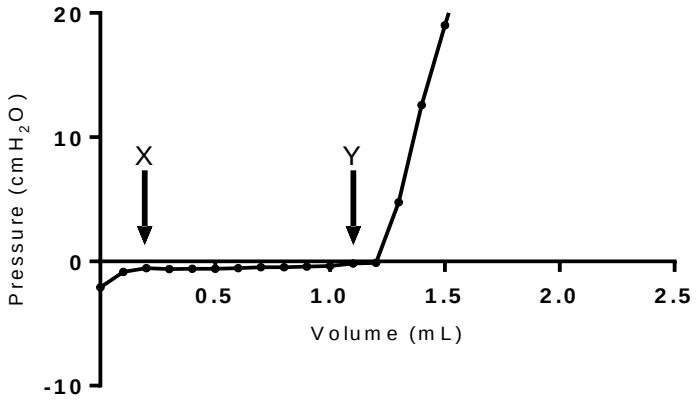
The measurement of transpulmonary and transdiapragmatic pressure requires placement of oesophageal and gastric balloons.[71] Following application of lubrication and local anaesthetic to the nasal passage a combined balloon

catheter is inserted and passed into the oesophagus and stomach, assisted by patient swallowing. Once the catheter is fully inserted both balloons are filed with 2mL of air and then aspirated to leave small residual volumes for pressure recording and attached to the pressure transducers. The catheter is slowly withdrawn until the P_{oes} value becomes negative during inspiration. The catheter is then further withdrawn ~10cm to mid oesophageal level. Correct positioning of the catheter is confirmed by ensuring that $P_{oes} \sim P_{ao}$ during a Mueller's manoeuvre (dynamic occlusion test).[266] The catheter is then secured to the nose to prevent movement during testing.

Pressure-volume characteristics of balloon catheters

The pressure within the balloon catheters during testing is transmitted to the differential pressure transducer via the residual air left within them. Large pressure swings can cause sizable volume changes and sufficient air is required to allow pressures to be accurately recorded. The pressure-volume characteristics of combined catheters (Guangzhou Yinghui Medical Science & Technology Company, Guangzhou, China) were tested as follows. Firstly the air was expelled from the balloon by submersion under water for 5 minutes. The balloon was sealed via a 3 way tap and removed and allowed to dry and then attached to the pressure transducer. Air was inserted in 0.1mL increments and the pressure reading obtained was recorded and plotted as shown in Figure 9.

Figure 9: Pressure-volume characteristics for combined catheter balloons

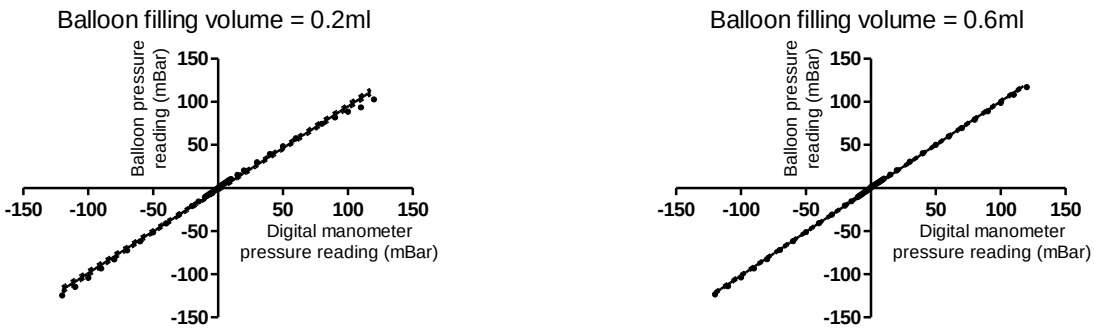


Testing indicated that the flat portion of the pressure-volume curve, between points X and Y on Figure 9, was between 0.2 and 1.2mL. To allow for sufficient volume change during testing 0.2mL was placed in the oesophageal balloon and 0.6mL in the gastric balloon.

Linearity of the balloon-catheter-transducer system

To test the balloon-catheter-transducer system to ensure it responded in a linear fashion to pressure changes the catheter was placed within a sealed bell jar. The pressure within the bell jar was altered in order to provide the range of pressures to be tested and the synchronous readings from the digital manometer and the balloon-catheter-transducer system were plotted allowing linearity to be demonstrated (Figure 10).

Figure 10: Balloon-catheter-transducer linearity testing at typical balloon filling volumes



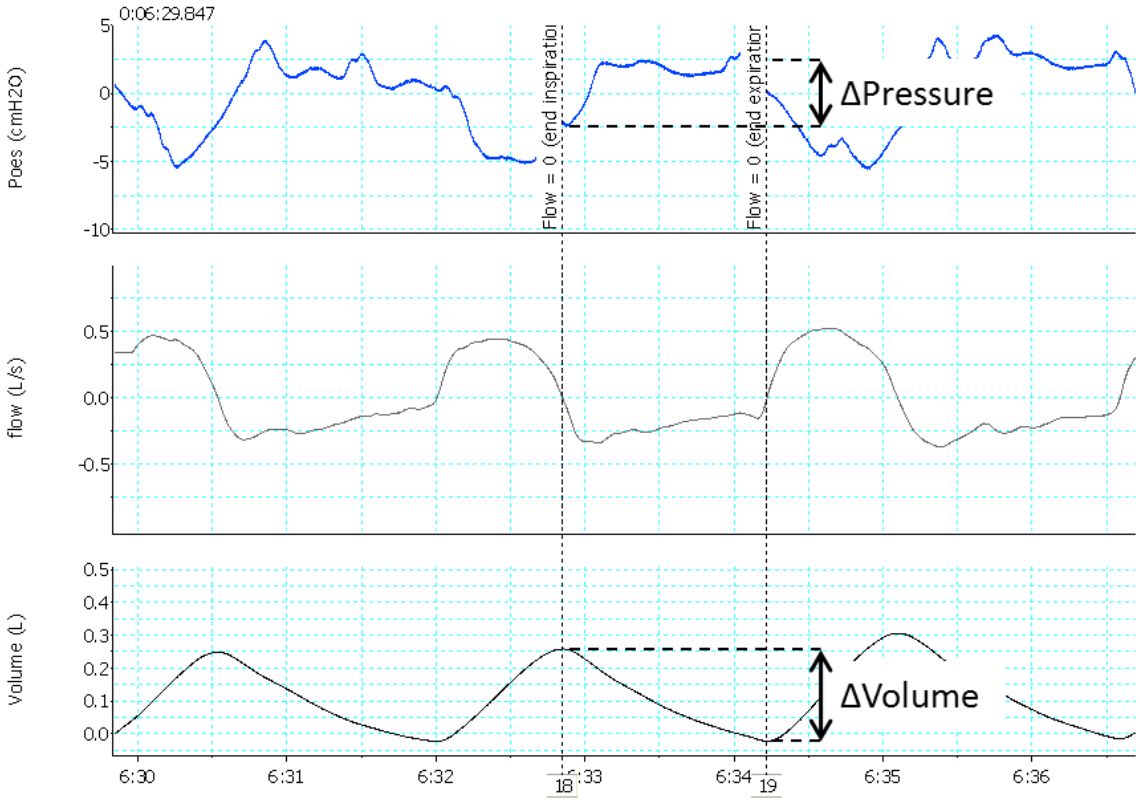
Measurement of flow

A heated pneumotachograph (model 3830, Hans-Rudolph, Shawnee, KS, US) was attached to a low pressure differential pressure transducer spirometer pod (ADInstruments, Chalgrove, UK). Standard operating conditions were maintained and calibration performed using a 3L volume syringe (Hans-Rudolph, Shawnee, KS, US) fitted to the pneumotach via a tight rubber seal after the spirometer pod was zeroed. Several loops were then performed with the calibration syringe at differing speeds to allow simulation of several flow rates. Accuracy of inspiratory and expiratory limbs were checked to ensure values were within 3% of the injected volume.

Static and dynamic compliance

The ease at which pressure changes across the respiratory system produce changes in volume is termed pulmonary compliance. It can be measured in either static or dynamic fashion. The measurement of static compliance requires specialist equipment and detailed coaching of patients whereas dynamic compliance can be readily calculated during tidal breathing. Dynamic compliance is measured during the expiratory phase by dividing the expiratory volume by the oesophageal pressure change from end inspiration to end expiration (Figure 11). The measurement is made during the relaxed expiratory phase to ensure that the reading is not influenced by respiratory muscle activity and the work required to overcome surface tension during inspiration.[267]

Figure 11: Measurement of dynamic compliance

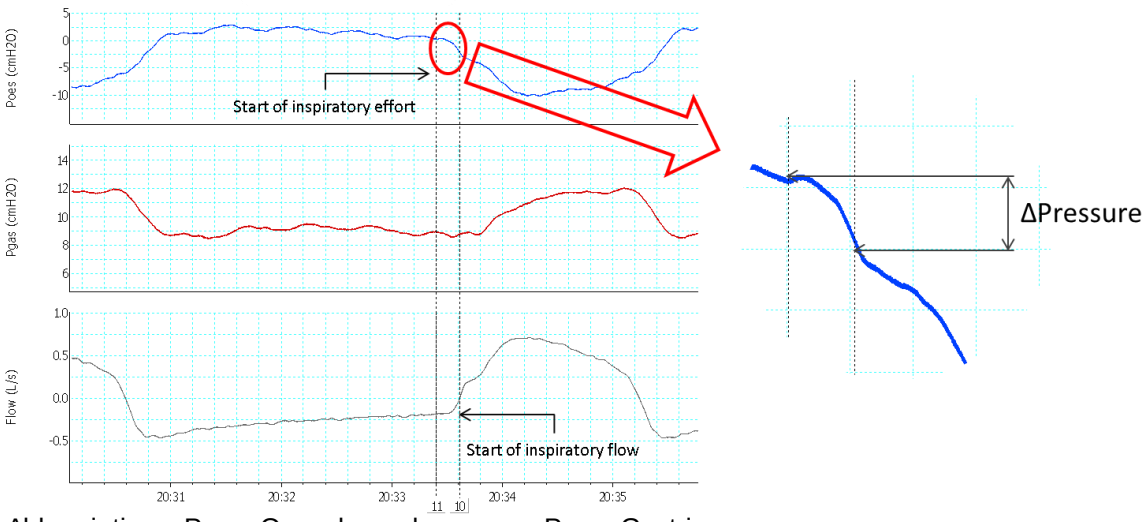


Abbreviations: P_{oes} – Oesophageal pressure

Intrinsic Positive end-expiratory pressure ($PEEP_i$)

As with compliance, $PEEP_i$ can be measured via static or dynamic tests. Dynamic $PEEP_i$ represents change in oesophageal pressure from the start of inspiratory effort, as denoted by a rapid fall in oesophageal pressure, to the start of inspiratory flow (Figure 12). This value represents the lowest regional value of PEEP that needs to be overcome in order to start inspiration and so can be an underestimate of static PEEP in diseases with considerable heterogeneity. This value should be corrected for active expiration by subtracting any rise in gastric pressure during the preceding expiratory phase from the value obtained.[66]

Figure 12: Measurement of dynamic intrinsic positive end-expiratory pressure



Abbreviations: P_{oes} – Oesophageal pressure, P_{gas} – Gastric pressure

3.6.3: Respiratory muscle strength

Non-invasive assessment of respiratory muscle strength (Sniff nasal inspiratory pressure (SNIP), maximum inspiratory pressure at the mouth (PI_{max}) and maximum expiratory pressure at the mouth (PE_{max}) were carried out using a handheld device (Micromedical Ltd, Kent, UK) in accordance with the American Thoracic Society-European Respiratory Society guidelines.[32] During measurement of advanced pulmonary mechanics a full range of respiratory muscle tests were completed including sniff, PI_{max}, PE_{max}, TLC, MVV and cough. These advanced tests provide more detailed information including global (sniff P_{oes}) and diaphragm specific (sniff P_{di}) measures of respiratory muscle strength.

3.6.4: Measures of respiratory drive

Respiratory drive can be measured during tidal breathing by normalising recorded respiratory muscle EMGs to the maximum achieved during respiratory manoeuvres. This normalised $EMG_{\%max}$ reduces the effect of between patient variation in skin preparation and subcutaneous tissue.

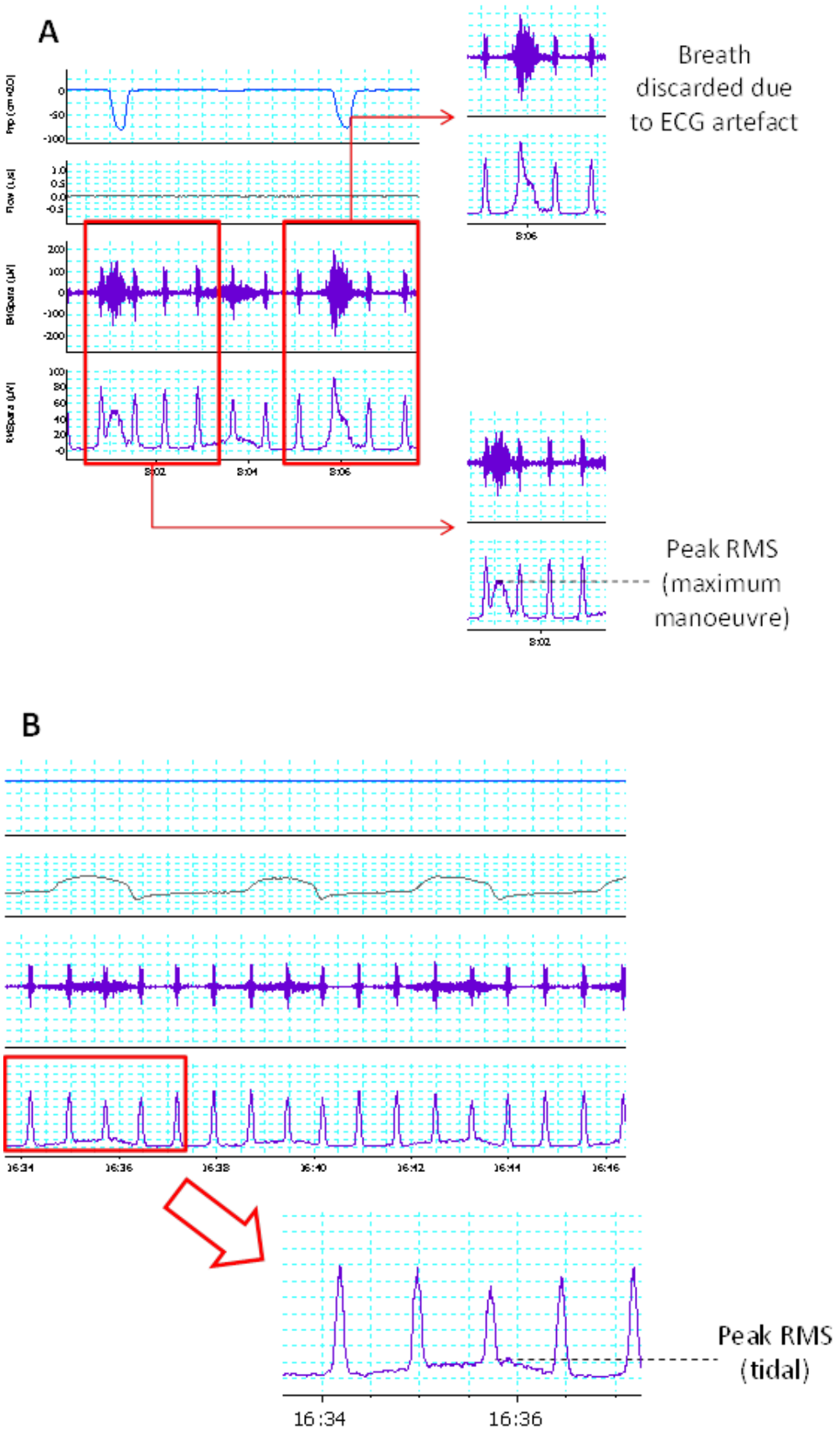
Measurement of parasternal muscle electromyogram (EMG_{para})

The second intercostal space was identified using bony landmarks and skin was prepared with EMG contact gel (Nuprep, DO Weaver and Co, US). Wet gel electrodes (Neuroline 720, Ambu, Denmark) were placed adjacent to the sternal

edge in the second intercostal spaces. The signal was amplified and processed using a high differential amplifier with band pass filters set at 10Hz and 2000Hz (1902, Cambridge Electronic Design, Cambridge, UK - St Thomas' Hospital site; Octbioamp, ADInstruments, Chalgrove, UK - Royal Brompton Hospital site). Additional analogue 50Hz notch filter and AC coupling were used. Amplified signals were passed to an analogue to digital convertor (Powerlab, ADInstruments, Chalgrove, UK) and then to a personal computer. Further digital filtering occurred at 20Hz after data acquisition (LabChart v7.2, ADInstruments, Chalgrove, UK). EMG_{para} recordings were performed with the patient relaxed in a chair or semi-recumbent in bed with arms supported. EMG_{para} signals were acquired during resting breathing for at least 5 minutes and until more than 2 minutes of stable breathing were recorded, a typical trace is provided in Figure 13.

As described earlier maximum manoeuvres were performed and used as the maximum EMG_{para} measurement. EMG_{para} signals were analysed using the root mean squared (RMS) of the raw EMG_{para} signal with a 40ms moving window and normalised to the maximum RMS EMG_{para} value ($EMG_{para\%max}$) analogous to the algorithm previously described for the analysis of EMG_{di}.[53] Peak RMS EMG_{para} was recorded for each breath, discarding those breaths which were contaminated by ECG artefacts. The value for each breath was normalised for the maximum RMS EMG_{para} obtained and the mean for all valid breaths was then calculated. Whilst $EMG_{para\%max}$ reflects neural drive per breath and has been used in stable patients we have also used a neural respiratory drive index (NRDI, arbitrary units; AU) that incorporated respiratory rate to develop a measurement of neural drive to the respiratory muscles per unit time.

Figure 13: Representative trace of raw data during [A] maximum sniff manoeuvre and [B] tidal breathing in a patient with stable Chronic Obstructive Pulmonary Disease

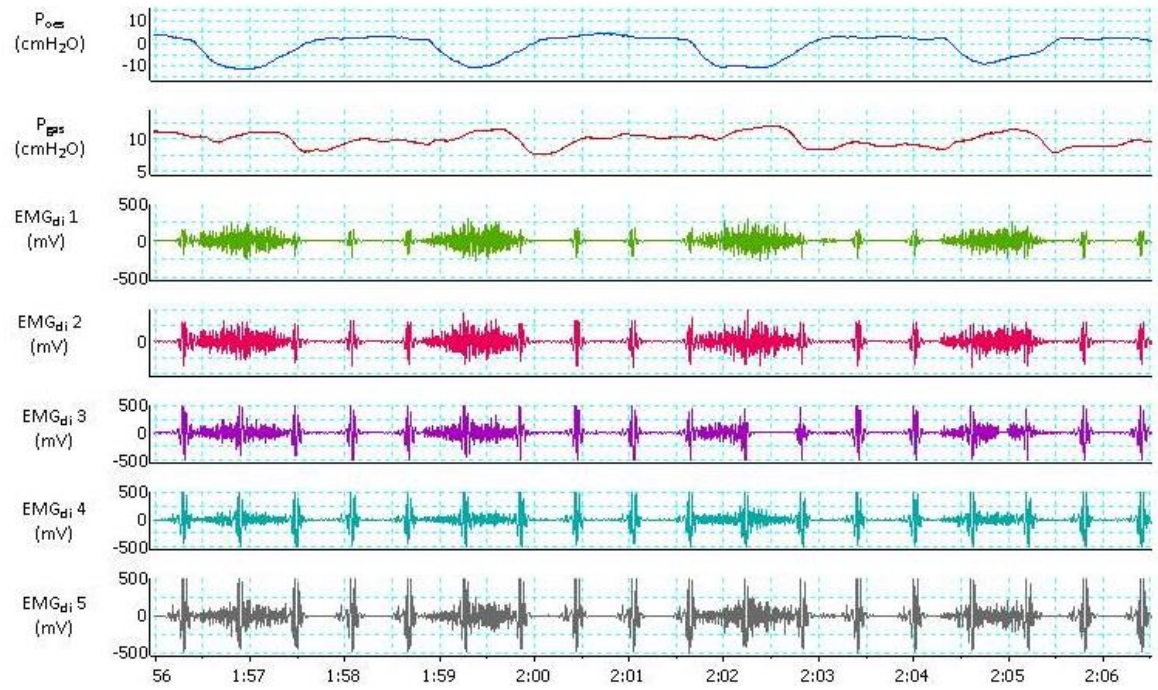


Abbreviations: Pnp – Nasopharyngeal pressure (cmH_2O, top row), Flow (l/s, 2nd row), EMG_{para} – Parasternal muscle electromyogram (µV, 3rd row), RMS – Root mean squared (µV, bottom row).

Measurement of diaphragm electromyogram (EMG_{di})

A combined respiratory pressure-EMG multipair electrode catheter was used which allows for reliable signals to be acquired across a range of lung volumes.[58] Catheter placement occurred as described earlier in this chapter. The raw EMG signals were amplified and processed as described above for EMG_{para} with the multipair design producing 5 channels of data. Positioning was optimised to ensure the largest raw EMG_{di} signals were obtained in the outermost channels. The channel with the largest RMS EMG_{di} signal for each breath was used to calculate the $EMG_{di\%max}$.

Figure 14: Example of invasive pulmonary physiology raw data obtained from combined balloon-electrode catheter to confirm catheter position



Abbreviations: P_{oes} – Oesophageal pressure, P_{gas} – Gastric pressure, EMG_{di} – diaphragm electromyogram.

Measurement of other surface electromyogram (EMG)

In addition to the obligatory inspiratory muscle EMGs recorded from the parasternal and diaphragm surface EMGs were acquired from the right sternocleidomastoid and right external oblique abdominal muscles. These

groups were chosen in order to obtain surface EMG signals from an accessory (sternocleidomastoid) and expiratory (abdominal) muscle. Bipolar electrodes were placed adjacent along the surface landmarks of the relevant muscle at 1/3 from the distal insertion point for the sternocleidomastoid muscle and 2/3 between umbilicus and anterior iliac crest for the external oblique abdominal muscle. Maximum EMG signals were obtained during the same inspiratory manoeuvres as the parasternal and diaphragm muscles for the sternocleidomastoid and during a cough and MEP manoeuvre for the abdominal muscles.

Hypercapnic challenge test

The HCVR was performed using a modified version of the technique originally described by Reed *et al*[234] and validated in COPD by our own group.[237] A simple circuit was employed to minimise dead space with mouth piece, pneumotacch, 3 way valve and 5L douglas bag placed in series. End-tidal CO_2 ($etCO_2$) measurements were performed using the Capnocheck sleep (Smith Medical, WI, US). Calibration was performed in line with manufacturer recommendations and delay from sampling port to output was checked prior to each testing and corrected digitally. Ventilatory parameters were calculated breath by breath for the duration of the test (4½ minutes or patient intolerance) with the first 30 seconds being discarded from analysis. A second run was performed following a minimum period of 30 minutes rest. Physiological recordings of respiratory muscles were performed during the hypercapnic challenge test and plotted via the same method as minute ventilation allowing slopes of $\Delta V_e/\Delta etCO_2$ and $\Delta EMG_{\%max}/\Delta etCO_2$ to be calculated using linear regression. The mean slope of 2 technically satisfactory runs was used. To be deemed technically satisfactory the runs must have been at least 1 minute in duration and demonstrated a linear increase in $etCO_2$ during testing of at least 1kPa. The results of technically inadequate tests were omitted. When the resultant slope of a technically satisfactory test was not demonstrably linear (via linear regression analysis) a value of 0 was entered to indicate that, within the limitations of testing, no response to hypercapnic challenge was present.

3.7: Assessment of Sleep Disordered Breathing

Due to the changes that occur in the respiratory load-capacity-drive relationship during sleep it was essential to complete patient assessments with measures during sleep.

3.7.1: Overnight oximetry-capnometry

A combined oximeter-capnometer device (Tosca 500, Radiometer, Crawley, West Sussex, UK) was used to measure oxygen saturations (SpO_2) and $tcCO_2$ during sleep. Capnometer probes were calibrated at the start and end of sleep monitoring and the data was uploaded to a personal computer using Download 2001 (Stowood Instruments, Beckley, Oxford, UK) allowing for the calculation of:

- 4% Oxygen desaturation index
- Mean SpO_2
- Minimum SpO_2
- Total analysis time with an SpO_2<90% (time and percentage)
- Mean $tcCO_2$
- Maximum $tcCO_2$

3.7.2: Advanced sleep studies

Respiratory polygraph

The diagnosis and severity of sleep disordered breathing (obstructive and central apnoea events and hypoventilation) was performed using the Embletta (Embla, Broomfield, CO, US). This is a multichannel device recording nasal flow, respiratory effort via inductance plethysmography, SpO_2, heart rate and body position. The device was set prior to each individual recording and a system check was performed once the patient set up was complete. At the end of the sleep study the device is downloaded via the Somnologica software (Embla, Broomfield, CO, US). Studies were individually scored detailing the frequency of obstructive apnoea events, central apnoea events and hypopnoea events.

Actigraphy

Wrist worn actigraphy is described earlier for the monitoring of physical activity. These devices are widely used for the monitoring of circadian rhythm disturbance in patients with respiratory sleep disorders.[268] They have been shown to correlate with polysomnogram derived sleep parameters[269] and have the advantage of providing domiciliary recordings over several days.[121] Daily rest periods were set as described earlier and subsequent analysis using commercial software (Actiware 5, Philips-Respironics, Murrysville, PA, US) produced values for:

- Total sleep time – Total duration, in minutes, of actigraphy defined sleep in the rest period, i.e. between lights off and lights on
- Wake after sleep onset – Total duration, in minutes, of actigraphy defined wake between sleep onset and lights on
- Sleep efficiency – Calculated as the percentage of a rest period with actigraphy defined sleep
- Sleep latency – Time, in minutes, between lights off and sleep onset

3.8: Set up of home oxygen therapy (HOT) and home mechanical ventilation (HMV) for HOT-HMV UK study

3.8.1: Home Oxygen Therapy (HOT)

All eligible patients had standardisation of medical therapy to ensure they received inhaler therapy with long acting β_2-agonist, steroid and long acting anti-muscarinic and nebulised or inhaled short acting β_2-agonist. Other medication, including oral theophylline remained unchanged and under the discretion of the usual care providers. Patients had arterial blood gases (ABGs) performed whilst seated and breathing room air for at least 20 minutes. ABGs for assessment of HOT were performed at least 4 hours after waking. Patients with hypoxia (PaO_2 < 7.3 kPa or PaO_2 < 8 kPa with features of secondary hypoxaemia) on ABGs performed at least 2 weeks following resolution of respiratory acidosis were deemed to meet the criteria for HOT.

Features of secondary hypoxaemia:

- Polycythaemia
- P-pulmonale on ECG
- Pulmonary hypertension
- Peripheral Oedema
- Nocturnal hypoxia (>30% sleep time with SpO_2 <90%)

A distinction is required between HOT and long term oxygen therapy (LTOT) with the latter requiring a longer period of clinical stability and repeat blood gases at least 3 weeks apart in order to qualify for treatment.[270] The rationale in using HOT as opposed to LTOT was that the study was specifically designed to look at a high risk recurrent exacerbator phenotype and previous data had shown that in the target population the median length of time to readmission was 32 days and so a significant proportion of patients would be readmitted before the period of stability would be reached and thus would never reach eligibility for the study.[271] Oxygen therapy was prescribed for both groups at the lowest flow able to correct daytime hypoxia (to achieve SpO_2 > 90% and PaO_2 > 8 kPa). Patients were advised to use HOT for at least 15 hours per day. All patients also received standardised education on oxygen therapy.

3.8.2: Home Mechanical Ventilation (HMV) setup

HMV setup was performed as an inpatient using either Harmony 2 machine (Philips-Respironics, Murrysville, PA, US) or VPAP III STa machine (ResMed, Bella Vista, Australia) using a standardised titration protocol (Appendix F: HOT-HMV titration protocol) to achieve high pressure ventilation (inspiratory positive airways pressure (IPAP) ≥ 25 cmH_2O) and control nocturnal sleep disordered breathing. The interface (nasal or full face) was selected according to patient preference. Patients were advised to use HMV for the duration of their night time sleep period with an aim of achieving greater than 6 hours nightly use.

CHAPTER 4: TARGETED TIDAL VOLUME PRESSURE SUPPORT VENTILATION VS. FIXED LEVEL PRESSURE VENTILATION IN SUPER OBESE PATIENTS WITH CHRONIC RESPIRATORY FAILURE

4.1: Materials and Methods

All subjects provided written informed consent prior to enrolment. The study was approved by Guy's research ethics committee (07/H0804/140) and the research was conducted in accordance with the declaration of Helsinki and local governance policies (RJ1 08/0074). The study was registered prospectively on a publically accessible database (ISRCTN63940700).

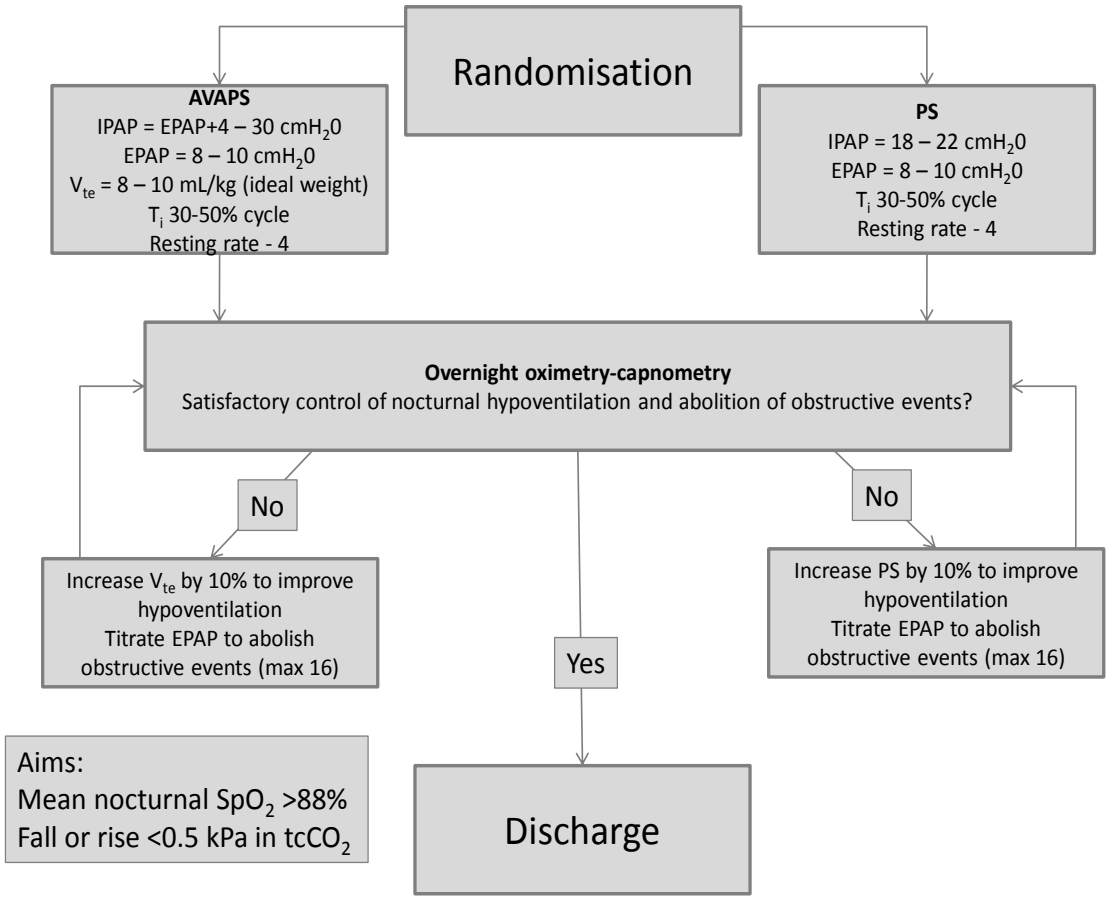
4.1.1: Study design

The study was a single (subject) blinded prospective randomised controlled trial. Patients were randomly allocated via minimisation to either standard care using nurse-led protocolised fixed bi-level Pressure Support NIV (PS) or the addition of AVAPS mode using a BiPAP synchrony device (Philips-Respironics, Murrysville, PA, US). Minimisation was performed using BMI (40-50 kg/m^2, 50-60 kg/m^2 or >60 kg/m^2), neck circumference (<45 / ≥45 cm), gender (male or female) and mode of referral (acute or elective) variables.

4.1.2: Patient assessment and treatment titration

Patients underwent baseline spirometry (microplus handheld spirometer, Cardinal Health, OH, US), arterial blood gases, anthropometrics including body composition (Bodystat 1500, Bodystat Ltd, Isle of Man, UK) and completed health related quality of life questionnaires (Severe Respiratory Insufficiency (SRI) Questionnaire, Epworth Sleepiness Score (ESS), Fatigue Severity Score (FSS) and Visual Analogue Score (VAS) for sleep comfort, fatigue and physical activity levels). Following randomisation patients underwent a titration of designated NIV mode using a predetermined protocol with settings altered according to the results of overnight oximetry-capnometry (Tosca 500, Radiometer, Crawley, UK), see Figure 15 and appendix G.

Figure 15: Non-invasive ventilation titration protocol for Average-Volume Assured Pressure Support (AVAPS) and fixed level Pressure Support (PS) arms



Patients were discharged on the allocated treatment and followed up at 3 months with repeat baseline investigations including overnight oximetry-capnometry on allocated treatment.

Patients had assessment of sleep disruption and daytime activity performed using the Actiwatch 64 (Philips-Respironics, Murrysville, PA, US), an accelerometer device that has been used previously to measure daytime activity in obesity[262] and to assess sleep patterns in respiratory sleep disorders[268]. Equipment limitations restricted the number of patients completing the actigraphy data collection section of the protocol. The accelerometer was worn for the 7 days following initiation of domiciliary NIV and the 7 days following the 3 month assessment.

4.1.3: Data analysis and statistics

To detect a difference in partial pressure of arterial carbon dioxide ($PaCO_2$) ≥ 0.5 kPa between intervention groups with a power of 80% at the 5% significance level required 42 patients to be randomised on a 1 to 1 basis. To allow for an approximate 20% drop out rate 50 patients were targeted for recruitment.

Data were analysed using independent or paired t-test where appropriate, unless data were demonstrably not normally distributed and then a non-parametric equivalent was used. For all analyses, a $p<0.05$ was considered statistically significant. Data analysis was conducted using PASW statistics 18 (SPSS, Chicago, IL, US).

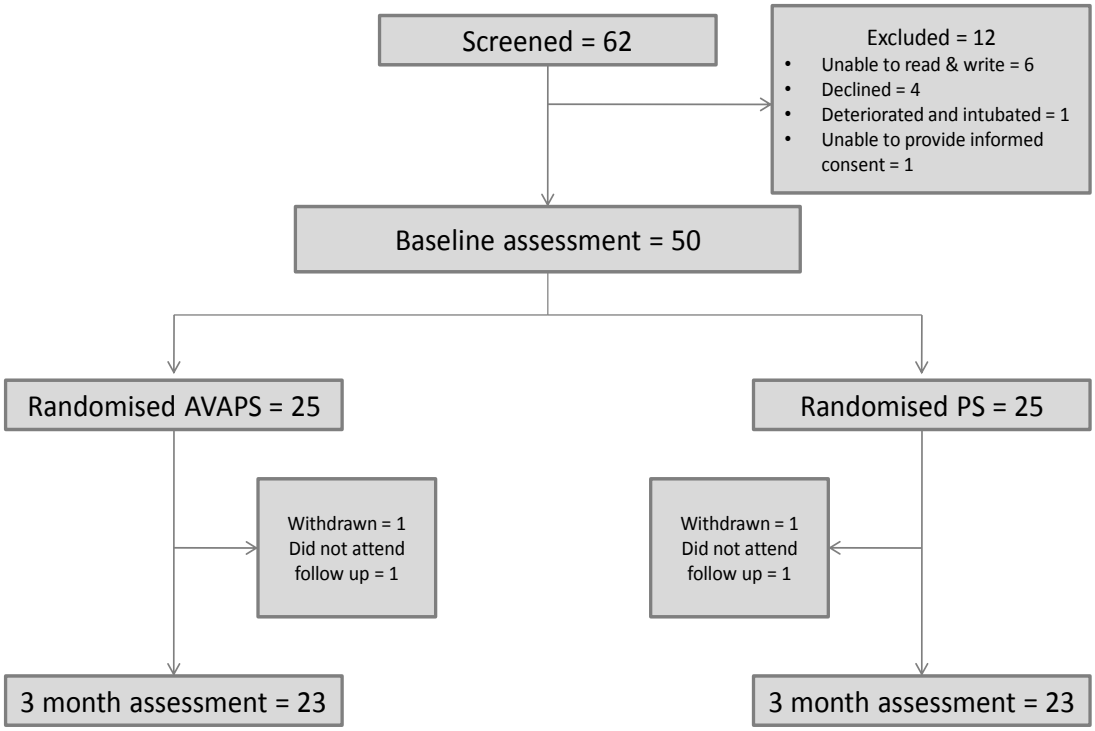
Multiple linear analysis was used to model the relationships between change in $PaCO_2$ and independent variables. The analysis used included the principal independent variable, compliance or estimated tidal volume per ideal body weight along with potential confounders. Variables selected to act as potential confounders for the analysis were treatment allocation, clinical presentation, gender and age.

Normally distributed data are presented as mean ± SD and not normally distributed data as median (range).

4.2: Results

62 patients were screened for study participation with 50 patients consented and randomised, of which 4 further patients (2 from either intervention group) were unable to be followed up in the study period. Further details are provided in Figure 16 of study exclusions and withdrawals.

Figure 16: Recruitment, exclusions and withdrawals summary for Average-Volume Assured Pressure Support (AVAPS) and fixed level Pressure Support (PS) trial



4.2.1: Baseline anthropometrics and sleep variables

No statistically significant differences were demonstrated in any assessed variable between randomised groups at baseline (Table 6).

Table 6: Baseline variables and treatment outcomes for Average-Volume Assured Pressure Support (AVAPS) and fixed level Pressure Support (PS) trial

	AVAPS			Fixed level PS		
	Baseline	**Follow up**	p-value	**Baseline**	**Follow up**	p-value
Age (years)	53 ± 9			56 ± 11		

	AVAPS			Fixed level PS		
	Baseline	**Follow up**	p-value	**Baseline**	**Follow up**	p-value
Gender (male / female)	12 / 13			11 / 14		
Presentation (Emergency / Elective)	9 / 16			9 / 16		
BMI (kg/m^2)	50 ± 8	48 ± 9	0.007	52 ± 8	51 ± 7	0.024
Fat Free Mass (kg)	69 ± 17	68 ± 18	0.493	72 ± 18	71 ± 18	0.870
Waist Circumference (cm)	141 ± 18	136 ± 17	0.006	145 ± 14	146 ± 14	0.120
Neck Circumference (cm)	46 ± 6	46 ± 7	0.340	48 ± 5	48 ± 7	0.084
FEV_1 (%predicted)	53 ± 15	59 ± 14	0.039	55 ± 15	60 ± 16	0.222
FVC (%predicted)	52 ± 14	58 ± 13	0.019	56 ± 15	62 ± 18	0.189
$PaCO_2$ (kPa)	7.0 ± 0.7	6.4 ± 0.8	0.004	6.8 ± 0.8	6.2 ± 0.8	0.021
PaO_2 (kPa)	8.9 ± 1.2	9.1 ± 1.2	0.660	8.7 ± 1.8	9.3 ± 1.2	0.163
HCO_3^- (mmol/l)	31 ± 3	29 ± 3	0.001	31 ± 4	27 ± 3	0.003

The p-values refer to paired t-test analysis from initiation to follow up values within each group. Abbreviations: BMI – body mass index, FEV_1 – forced expiratory volume in 1s, FVC – forced vital capacity, $PaCO_2$ – arterial partial pressure of carbon dioxide, PaO_2 – arterial partial pressure of oxygen, HCO_3^- – serum bicarbonate.

4.2.2: Treatment titration

The median time to achieve satisfactory NIV setup was 2 days (range 1-4 days) for both groups. Nocturnal ventilatory control, assessed by overnight oximetry and $tcCO_2$, was similar in both the AVAPS and fixed level PS groups (Table 7). Three patients failed to reach the predetermined criteria for satisfactory ventilator setup (2/25 PS vs. 1/25 AVAPS; p=0.6) due to an inability to tolerate the increase in inspiratory positive airways pressure (IPAP) or tidal volume (V_{te}). These patients were discharged on the highest tolerated settings.

Supplementary oxygen was required by six patients (4/25 PS vs. 2/25 AVAPS; p=0.4).

Table 7: Discharge oximetry-capnometry results in Average-Volume Assured Pressure Support (AVAPS) and fixed level Pressure Support (PS) groups

	AVAPS	**Fixed level PS**	p-value
4%ODI (events/hour)	22 ± 16	22 ± 17	0.517
Mean SpO_2 (%)	92 ± 3	92 ± 3	0.552
%TST SpO_2 <90% (%)	20 ± 21	15 ± 20	0.630
Mean $tcCO_2$ (kPa)	7.1 ± 0.7	7.2 ± 1.0	0.952
Max $tcCO_2$ (kPa)	8.4 ± 0.8	8.4 ± 1.6	0.980

The p-value refers to comparison between interventions by independent t-test. Abbreviations: ODI – oxygen desaturation index, SpO_2 – oxyhaemaglobin saturation, TST – total sleep time, $tcCO_2$ – transcutaneous carbon dioxide.

At discharge, ventilator settings provided a mean IPAP 25 ± 3 cmH_2O in the PS group and mean V_{te} 657 ± 96 mL in the AVAPS group. A small but statistically significant difference in mean EPAP was present with 10 ± 2 and 9 ± 1 cmH_2O in the PS and AVAPS groups respectively (p=0.03). Mean back up rate was 14 ± 1 breaths per minute in both groups.

4.2.3: Actigraphy assessed sleep and activity parameters following initiation of NIV

No significant differences were demonstrated between AVAPS and PS groups in objective assessment of sleep quality (total sleep time (TST), wake after sleep Onset (WASO), sleep efficiency or sleep latency) at baseline or follow up (Table 8).

Table 8: Actigraphy analysed sleep parameters for the 1st week following initiation of non-invasive ventilation compared with the 1st week following the 3 month assessment in the Average-Volume Assured Pressure Support (AVAPS) (n=14) and fixed level Pressure Support (PS) (n=15) arms

	Baseline			Follow up		
	AVAPS	**Fixed level PS**	p-value	**AVAPS**	**Fixed level PS**	p-value
TST (minutes)	341 ± 80	352 ± 78	0.713	321 ± 52	346 ± 75	0.302
WASO%TST (%)	23 ± 11	23 ± 17	0.987	27 ± 16	20 ± 13	0.185
Latency (minutes)	5 ± 3	8 ± 7	0.164	4 ± 2	5 ± 6	0.577
Efficiency (%)	80 ± 7	80 ± 13	0.894	79 ± 9	81 ± 9	0.416

The p-value refers to comparison between interventions at each time point by independent t-test. Abbreviations: TST – total sleep time, WASO – wake after sleep onset.

4.2.4: Outcome following 3 months of domiciliary NIV

Gas exchange, health related quality of life, daytime somnolence and control of sleep disordered breathing

There were no between group differences in change in the primary outcome: $PaCO_2$, or secondary outcomes: daytime gas exchange, anthropometric measures, spirometry, HRQL or daytime somnolence (Table 9, Table 10).

Table 9: Changes in gas exchange, anthropometrics and spirometry between non-invasive ventilation initiation and follow up

	AVAPS	**Fixed level PS**	Mean difference between treatments (95%CI)	p-value
$\Delta PaCO_2$ (kPa)	-0.6 ± 1.0*	-0.6 ± 1.1*	0 (-0.7 to 0.6)	0.867
ΔPaO_2 (kPa)	0.2 ± 1.7	0.5 ± 1.6	0 (-1 to 1)	0.519
ΔHCO_3^- (mmol/L)	-3 ± 3*	-3 ± 4*	0 (-2 to 2)	0.825

	AVAPS	Fixed level PS	Mean difference between treatments (95%CI)	p-value
ΔBMI (kg/m^2)	-1 ± 2*	-2 ± 4*	1 (-1 to 2)	0.497
ΔFat free mass (kg)	-1 ± 6	0 ± 8	-1 (-4 to 3)	0.805
ΔWaist circumference (cm)	-3 ± 5*	-2 ± 7	-1 (-3 to 4)	0.676
ΔFEV_1 (%predicted)	6 ± 13*	4 ± 14	2 (-6 to 10)	0.588
ΔFVC (%predicted)	6 ± 12*	5 ± 17*	1 (-7 to 10)	0.777

The p-value refers to comparison between interventions by independent t-test, * indicates a significant ($p<0.05$) within group imporvement. Abbreviations: $PaCO_2$ – arterial partial pressure of carbon dioxide, PaO_2 – arterial partial pressure of oxygen, HCO_3^- – serum bicarbonate, BMI – body mass index, FEV_1 – forced expiratory volume in 1s, FVC – forced vital capacity.

Table 10: Between treatment group comparison of changes in health related quality of life and daytime somnolence from initiation of non-invasive ventilation to follow up at 3 months

	AVAPS	Fixed level PS	Mean difference between treatments (95%CI)	p-value
ΔSRI-SS (/100)	11	7	5 (-2 to 12)	0.212
ΔSRI-RC (/100)	15	11	4 (-8 to 16)	0.464
ΔSRI-PF (/100)	8	5	3 (-7 to 14)	0.532
ΔSRI-AS (/100)	15	6	9 (-2 to 20)	0.121
ΔSRI-SR (/100)	5	6	0 (-11 to 10)	0.927
ΔSRI-AX (/100)	17	9	8 (-6 to 22)	0.260

	AVAPS	Fixed level PS	Mean difference between treatments (95%CI)	p-value
∆SRI-WB (/100)	9	4	5 (-5 to 14)	0.338
∆SRI-SF (/100)	13	8	5 (-8 to 14)	0.429
∆VAS-sleep comfort (/100)	13	20	8 (-8 to 23)	0.332
∆VAS-activity (/100)	8	0	-9 (-26 to 9)	0.324
∆VAS-fatigue (/100)	19	13	-6 (-23 to 11)	0.480
∆ESS (/24)	-5	-6	1 (-2 to 5)	0.428
∆FSS (/56)	-9	-7	-2 (-11 to 8)	0.752

SRI: higher score indicates better quality of life, VAS: higher score indicates greater quality of life; FSS: higher score indicates greater level of fatigue. The p-value refers to comparison between interventions by independent t-test. Abbreviations: SRI-SS – severe respiratory insufficiency questionnaire summary score, SRI-RC – severe respiratory insufficiency questionnaire respiratory complaints domain, SRI-PF – severe respiratory insufficiency questionnaire physical function domain, SRI-AS – severe respiratory insufficiency questionnaire attendant symptoms and sleep domain, SRI-SR – severe respiratory insufficiency questionnaire social relationships domain, SRI-AX – severe respiratory insufficiency questionnaire anxiety, SRI-WB – severe respiratory insufficiency questionnaire well-being domain, SRI-SF – severe respiratory insufficiency questionnaire social functioning, VAS – visual analogue score, ESS – Epworth sleepiness score, FSS – fatigue severity score.

Significant within group improvements occurred in $PaCO_2$, health related quality of life, daytime somnolence and overnight oximetry-capnometry (Table 6, Table 11 and Figure 17) between baseline and follow up. Change in daytime $PaCO_2$ strongly correlated with other clinically important and patient relevant outcomes including change in anthropometrics (Δweight r=0.438, p=0.002; ΔFM r=0.619, p<0.001; Δwaist circumference r=0.339, p=0.021; ΔFFM r=-0.464, p=0.001), nocturnal hypoventilation (Δmean SpO_2 r=-0.310, p=0.043; Δmean $tcCO_2$

r=0.588, p<0.001), spirometry (ΔFEV_1 r=-0.470, p=0.001; ΔFVC r=-0.403, p=0.006) and HRQL (ΔSRI-SS r=-0.321, p=0.029).

Figure 17: Comparison of inter and intra group changes in Average-Volume Assured Pressure Support (AVAPS) and fixed level Pressure Support (PS) for [A] mean nocturnal oxyhaemoglobin saturation (SpO_2), [B] percentage nocturnal recording time with an SpO_2 <90%, [C] mean transcutaneous carbon dioxide ($tcCO_2$) and [D] max transcutaneous carbon dioxide $tcCO_2$

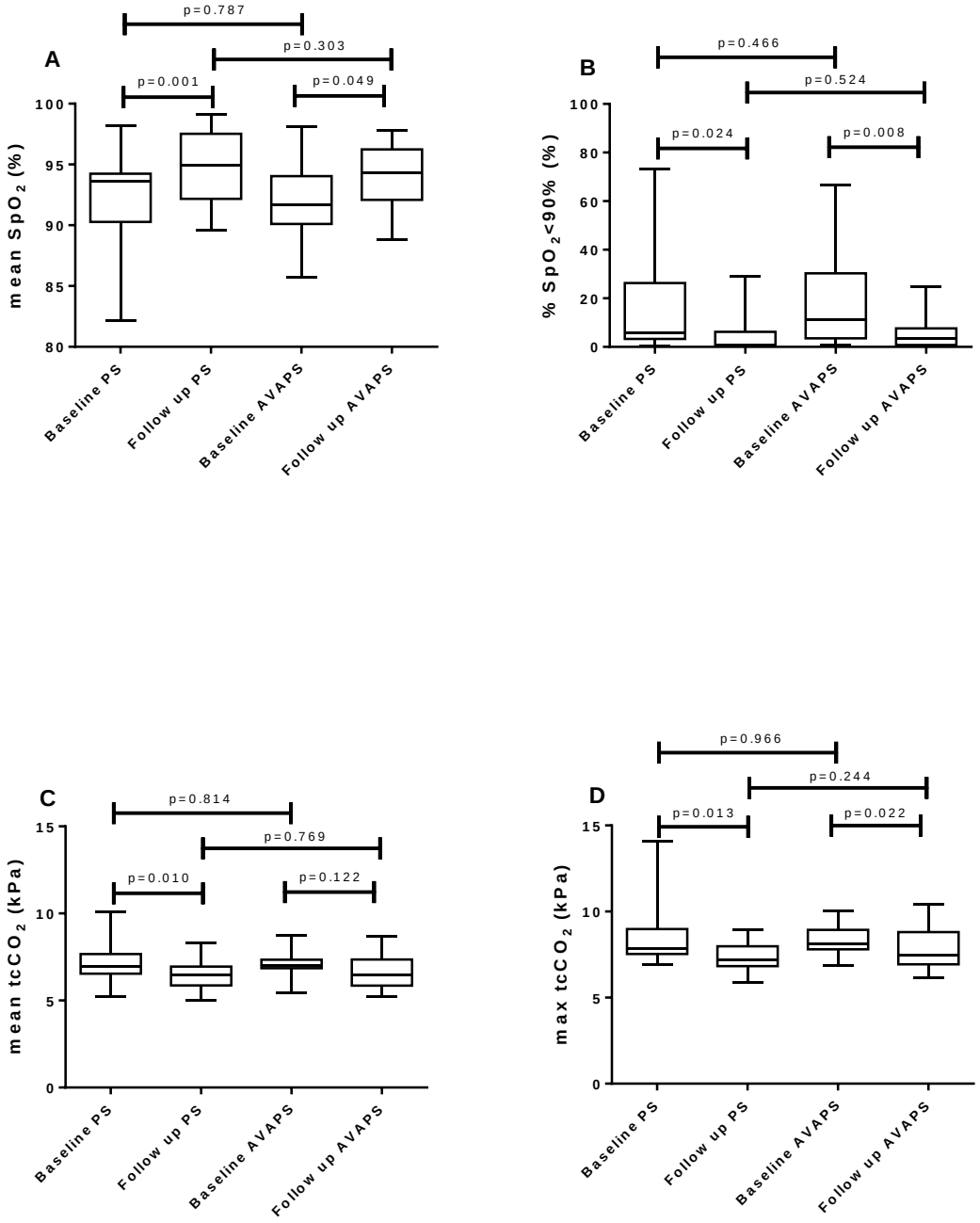


Table 11: Health related quality of life pre-post treatment in Average-Volume Assured Pressure Support (AVAPS) and Pressure Support (PS) groups

	AVAPS			Fixed level PS		
	Baseline	**Follow up**	p-value	**Baseline**	**Follow up**	p-value
SRI-SS (/100)	55 ± 16	66 ± 19	<0.001	51 ± 14	57 ± 15	0.018
SRI-RC (/100)	55 ± 20	70 ± 20	0.001	49 ± 24	59 ± 22	0.025
SRI-PF (/100)	50 ± 24	58 ± 26	0.069	42 ± 20	47 ± 22	0.139
SRI-AS (/100)	48 ± 17	62 ± 20	0.003	48 ± 19	54 ± 16	0.100
SRI-SR (/100)	66 ± 20	72 ± 24	0.116	67 ± 20	73 ± 18	0.165
SRI-AX (/100)	48 ± 24	65 ± 29	0.001	41 ± 23	50 ± 21	0.094
SRI-WB (/100)	55 ± 19	64 ± 21	0.007	51 ± 16	55 ± 17	0.303
SRI-SF (/100)	61 ± 24	73 ± 20	0.005	55 ± 22	63 ± 22	0.143
VAS-sleep comfort (/100)	44 ± 30	57 ± 27	0.026	33 ± 27	53 ± 22	0.001
VAS-activity (/100)	43 ± 24	52 ± 26	0.177	47 ± 23	47 ± 22	0.967
VAS-fatigue (/100)	39 ± 23	59 ± 27	0.001	42 ± 26	55 ± 28	0.058
ESS (/24)	11 ± 5	6 ± 5	0.001	13 ± 6	7 ± 5	<0.001
FSS (/56)	43 ± 14	34 ± 15	0.014	45 ± 16	37 ± 18	0.038

SRI: higher score indicates better quality of life, VAS: higher score indicates greater quality of life; FSS: higher score indicates greater level of fatigue. The p-values refer to paired t-test analysis from initiation to follow up values within each group. Abbreviations: SRI-SS – severe respiratory insufficiency questionnaire summary score, SRI-RC – severe respiratory insufficiency questionnaire respiratory complaints domain, SRI-PF – severe respiratory insufficiency questionnaire physical function domain, SRI-AS – severe respiratory insufficiency questionnaire attendant symptoms and sleep domain, SRI-SR – severe respiratory insufficiency

questionnaire social relationships domain, SRI-AX – severe respiratory insufficiency questionnaire anxiety, SRI-WB – severe respiratory insufficiency questionnaire well-being domain, SRI-SF – severe respiratory insufficiency questionnaire social functioning, VAS – visual analogue score, ESS – Epworth sleepiness score, FSS – fatigue severity score.

Ventilatory parameters

There were no between group differences in any of the assessed outcome variables (Table 6) or ventilator parameters (Table 12).

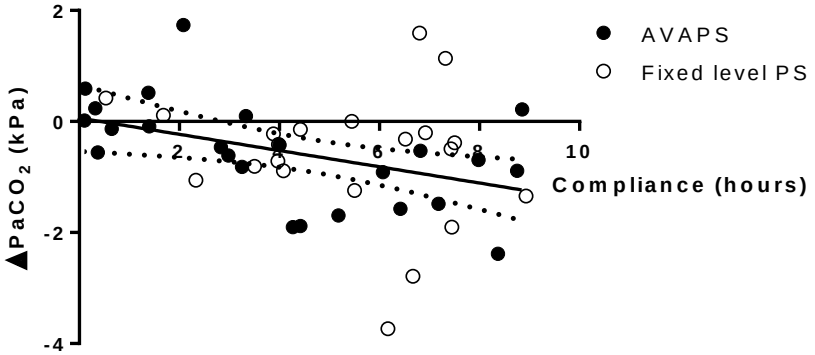
Table 12: Ventilator parameters at follow up in Average-Volume Assured Pressure Support (AVAPS) and fixed level Pressure Support (PS) groups

	AVAPS	**Fixed level PS**	p-value
Delivered IPAP (cmH_2O)	22 ± 5	23 ± 4	0.402
Leak (L/min)	53 ± 13	53 ± 19	0.968
Patient triggered breaths (%)	43 ± 27	45 ± 27	0.759
Compliance (hours:minutes/day)	4:11 ± 2:53	5:08 ± 2:22	0.230

Abbreviations: IPAP – inspiratory positive airway pressure.

NIV showed a dose response effect with a significant correlation between hours of use and improvement in daytime $PaCO_2$ (r=-0.370; p=0.012) with the 95% confidence interval crossing below 0 with an adherence time of 4 hours (Figure 18).

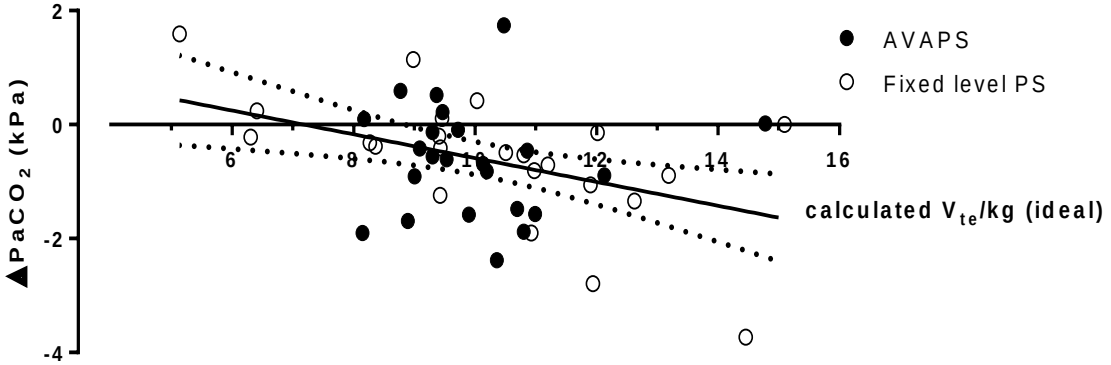
Figure 18: Relationship between ventilator compliance and change in arterial partial pressure of carbon dioxide ($PaCO_2$)



Abbreviations: AVAPS – average-volume assured pressure support, PS – fixed level pressure support.

A significant linear relationship was demonstrated when comparing the ventilator calculated mean V_{te} over the trial period per ideal body weight and the change in daytime $PaCO_2$ (r=-0.398; p=0.006) from baseline to follow up (Figure 19). Multiple linear regression analysis demonstrated no significant relationship between any of the potential confounders (treatment allocation, clinical presentation, age and gender) and change in $PaCO_2$. The model showed both ventilator adherence and V_{te} per ideal body weight were significantly related to change in $PaCO_2$.

Figure 19: Relationship between change in arterial partial pressure of carbon dioxide ($PaCO_2$) during trial period and calculated ventilation per unit of ideal body weight



Abbreviations: AVAPS – average-volume assured pressure support, PS – fixed level pressure support, V_{te} – ventilator estimated tidal volume.

Anthropometrics and physical activity

32 patients completed actigraphy monitoring analysis at baseline and 28 patients at follow up. There were no differences between the AVAPS and fixed level PS group at either baseline or follow up in measures of daytime physical activity and anthropometric variables (Table 13).

Table 13: Changes in actigraphy (n=28) and anthropometric (n=46) variables between baseline and 3 months follow up in treatment groups

	AVAPS	Fixed level PS	Mean difference between treatments (95%CI)	p-value
ΔWeight (kg)	-3 ± 5	-5 ± 9	2 (-2 to 7)	0.289
ΔFat free mass (kg)	-1 ± 6	0 ± 8	-1 (-5 to 4)	0.805
ΔFat mass (kg)	-2 ± 7	-4 ± 12	2 (-4 to 8)	0.484
ΔWaist circumference (cm)	-3 ± 5	-2 ± 7	-1 (-4 to 2)	0.676
ΔMean activity counts (counts/day)	18 ± 64	46 ± 64	-28 (-78 to 22)	0.261
ΔMax activity counts (counts/day)	207 ± 557	414 ± 506	-207 (-624 to 209)	0.315
ΔImmobile time (minutes/day)	-39 ± 96	-41 ± 90	2 (-70 to 75)	0.947
ΔMobile time (minutes/day)	4 ± 93	24 ± 79	-20 (-88 to 48)	0.545

4.2.5: Combined Average-Volume Assured Pressure Support (AVAPS) and fixed level Pressure Support (PS) cohort

As there were no clinically significant differences demonstrated between the AVAPS and fixed level PS modes in either primary or secondary outcomes, a single cohort (n=28) was produced to allow a *post-hoc* analysis of the relationship between physical activity and NIV in OHS patients.

Physical activity and weight loss

Baseline data showed that patients spent an average of 3 hours 21 minutes ± 1 hour 33 minutes immobile or asleep during the daytime period. There were significant inverse correlations observed between daytime activity (mean activity counts per day), and weight (r=-0.392; p=0.024) and waist circumference (r=-0.423; p=0.014). Significant reductions in weight, fat mass and waist

circumference were observed following 3 months of NIV, with an associated increase in physical activity (Table 14).

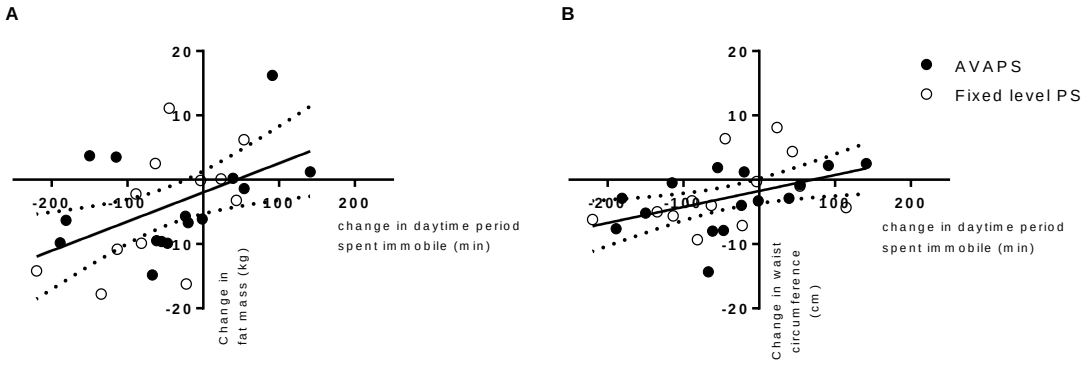
Table 14: Actigraphy (n=28) and anthropometric variables (n=46) at baseline and 3 months follow up

	Baseline	**Follow up at 3 months**	p-value
Weight (kg)	141 ± 28	137 ± 28	0.001
Fat free mass (kg)	70 ± 17	69 ± 17	0.593
Fat mass (kg)	70 ± 21	67 ± 19	0.041
Waist circumference (cm)	142 ± 15	140 ± 16	0.003
Mean activity counts (counts/day)	232 ± 100	263 ± 94	0.016
Max activity counts (counts/day)	1797 ± 507	2100 ± 553	0.006
Immobile time (minutes/day)	201 ± 93	161 ± 84	0.028
Mobile time (minutes/day)	771 ± 86	785 ± 110	0.417

Actigraphy analysed for the 1st week at home following initiation of NIV compared with the 1st week following the 3 month assessment of NIV.

There were significant correlations between change in physical activity, as measured by change in immobile time, and both the change in fat mass (r=0.482; p=0.011) and waist circumference (r=0.456; p=0.015) between baseline and follow up assessment (Figure 20).

Figure 20: Regression analysis showing relationship between change in anthropometric measures ([A] fat mass, [B] waist circumference) and change in physical activity between initation of NIV and 3 month follow up



Abbreviations: AVAPS – average-volume assured pressure support, PS – fixed level pressure support.

4.2.6: Ventilator Triggering

Post hoc analysis of ventilator triggering was performed using data downloaded from ventilator data cards at the end of the study period. An arbitrary cut off of ≤50% and >50% non-triggered ventilator delivered breaths was selected to investigate the effect of back up rate pressure controlled ventilation (PCV) dependency on clinical outcome. Baseline data for the groups is provided below in Table 15.

Table 15: Comparison between patients receiving ≤50% pressure control ventilation (PCV) and those patients receiving >50% PCV at baseline i.e. patient triggering greater than 50% of ventilator delivered breaths vs. less than 50% of ventilator delivered breaths

	PCV ≤50% n=17	**PCV >50% n=29**	p-value
Age (years)	52 ± 9	56 ± 11	0.277
Gender (male / female)	7 / 10	16 / 13	0.840
$PaCO_2$ (kPa)	6.6 ± 0.4	7.1 ± 0.8	0.018
BMI (kg/m^2)	52 ± 8	51 ± 8	0.669
FEV_1 (% predicted)	57 ± 15	54 ± 15	0.558
FVC (%predicted)	53 ± 17	52 ± 15	0.791

	PCV ≤50% n=17	PCV >50% n=29	p-value
ESS	11 ± 6	13 ± 6	0.400
SRI - SS	51 ± 16	54 ± 16	0.532
Mean nocturnal SpO_2 (%)	93 ± 3	92 ± 3	0.105
Mean nocturnal $tcCO_2$ (kPa)	7.0 ± 0.8	7.2 ± 0.9	0.593

Abbreviations: PCV – pressure controlled ventilation, $PaCO_2$ – arterial partial pressure of carbon dioxide, BMI – body mass index, FEV_1 – forced expiratory volume in 1s, FVC - forced vital capacity, ESS – Epworth sleepiness score, SRI-SS – severe respiratory insufficiency questionnaire summary score.

The ventilator settings were similar at NIV initiation in each group as shown in Table 16.

Table 16: Comparison of ventilator settings between patients receiving ≤50% pressure control ventilation (PCV) and those patients receiving >50% PCV at initiation of on-invasive ventilation (NIV)

	PCV ≤50%	PCV >50%	p-value
IPAP (cmH_2O)	23 ± 3	26 ± 3	0.052
EPAP (cmH_2O)	9 ± 1	10 ± 2	0.047
V_{te} (mL)	619 ± 75	661 ± 96	0.301
Back up rate (bpm)	14 ± 1	14 ± 1	0.223

Abbreviations: PCV – pressure controlled ventilation, IPAP – inspiratory positive airways pressure, EPAP – expiratory positive airways pressure, V_{te} – estimated tidal volume

Comparative *post hoc* analysis showed that patients with a backup rate PCV dependency >50% had a greater control of nocturnal carbon dioxide, improved daytime carbon dioxide and enhanced health-related quality of life at 3 months (Table 17). These data support the hypothesis that controlled NIV provides better nocturnal ventilatory control and improves patient outcome.

Table 17: Comparison of changes in gas exchange, anthropometrics, health-related quality of life and overnight oximetry-capnometry from baseline to 3 months in patients

receiving ≤50% pressure control ventilation (PCV) and those patients receiving >50% PCV

	PCV ≤50% n=17	PCV>50% n=29	Mean difference between groups (95%CI)	p-value
∆$PaCO_2$ (kPa)	-0.1 ± 0.7	-1.0 ± 1.1	0.9 (0.3 to 1.5)	0.003
∆BMI (kg/m^2)	-0.3 ± 1.5	-2.2 ± 3.2	1.9 (0.2 to 3.6)	0.031
∆ESS	-2 ± 5	-8 ± 6	6 (2 to 9)	0.001
∆SRI - SS	3 ± 11	13 ± 12	-10 (-2 to -17)	0.010
∆Mean nocturnal SpO_2 (%)	3 ± 6	5 ± 4	-2 (-5 to 1)	0.146
∆Mean nocturnal $tcCO_2$ (kPa)	-0.3 ± 0.8	-0.9 ± 1.2	0.6 (0.0 to 1.3)	0.049

Abbreviations: PCV – pressure controlled ventilation, $PaCO_2$ – arterial partial pressure of carbon dioxide, BMI – body mass index, ESS – Epworth sleepiness score, SRI-SS – severe respiratory insufficiency questionnaire summary score, SpO_2 – oxyhaemaglobin saturation, $tcCO_2$ – transcutaneous carbon dioxide.

4.2.7: Clinical Presentation

NIV Initiation

Patients presenting acutely had similar baseline anthropometrics, but with a greater restrictive ventilatory defect on spirometry and more pronounced hypercapnia compared to those patients admitted electively for NIV set up (Table 18).

Table 18: Baseline data based on elective or acute clinical presentation

	Elective (n = 33)	Acute (n = 17)	p-value
Treatment allocation (AVAPS / PS)	17 / 16	8 / 9	0.765
Age (years)	53 ± 10	58 ± 12	0.103

	Elective (n = 33)	Acute (n = 17)	p-value
Gender (Male / Female)	16 / 17	11 / 6	0.276
BMI (kg/m^2)	51 ± 8	51 ± 8	0.830
Fat Free Mass (kg)	71 ± 18	71 ± 20	0.944
Waist Circumference (cm)	140 ± 14	149 ± 19	0.079
Neck Circumference (cm)	47 ± 5	48 ± 6	0.348
FEV_1 (%predicted)	57 ± 13	47 ± 16	0.017
FVC (%predicted)	57 ± 12	49 ± 16	0.056
$PaCO_2$ (kPa)	6.7 ± 0.6	7.3 ± 0.8	0.004
PaO_2 (kPa)	8.7 ± 1.1	8.9 ± 2.2	0.796
HCO_3^- (mmol/l)	30 ± 3	32 ± 4	0.149

Abbreviations: AVAPS – average-volume assured pressure support, PS – fixed level pressure support, BMI – body mass index, FEV_1 – forced expiratory volume in 1s, FVC - forced vital capacity, $PaCO_2$ – arterial partial pressure of carbon dioxide, PaO_2 – arterial partial pressure of oxygen, HCO_3^- - serum bicarbonate.

However, the differences in both gas exchange and spirometry present at baseline were no longer significant at 6 week (p=0.36) and 3 month (p=0.94) follow up. There were no significant differences between acute and elective groups in terms of length of time to setup (AVAPS 2 day ± 1 day vs. PS 2 day ± 1 day; p=0.4) or respiratory sleep study measures (Table 19).

Table 19: Comparison of limited attended respiratory polygraphy data for elective and acute clinical presentation at initiation of non-invasive ventilation (NIV)

	Elective (n = 33)	Acute (n = 17)	p-value
4%ODI (events/hour)	25 ± 18	17 ± 10	0.085
Mean SpO_2 (%)	93 ± 3	91 ± 3	0.137

	Elective (n = 33)	Acute (n = 17)	p-value
%TST SpO_2 <90% (%)	18 ± 23	16 ± 15	0.708
Mean $tcCO_2$ (kPa)	6.7 ± 0.7	7.4 ± 1	0.061
Max $tcCO_2$ (kPa)	8.2 ± 0.8	8.8 ± 1.8	0.120

Abbreviations: ODI – oxygen desaturation index, SpO_2 – oxyhaemaglobin saturation, TST – total sleep time, $tcCO_2$ – transcutaneous carbon dioxide.

Variation in health-related quality of life

Paradoxically, despite greater disease severity, patients presenting following an acute decompensated episode of respiratory failure reported better levels in some health-related quality of life measures at enrolment. Subsequently patient initiated on treatment following an acute exacerbation had larger improvements in some of these measures at follow up compared with those patients presenting electively (Table 20).

Table 20: Health-related quality of life analysed according to elective and acute clinical presentation

	Elective			Acute		
	Baseline (n=33)	**Follow up (n=32)**	p-value	**Baseline (n=17)**	**Follow up (n=14)**	p-value
SRI-SS (/100)	51 ± 17	58 ± 17	0.002	57 ± 11	71 ± 15#	0.003
SRI-RC (/100)	48 ± 22	61 ± 21	<0.001	62 ± 19#	74 ± 21#	0.094
SRI-PF (/100)	49 ± 23	51 ± 25	0.451	40 ± 18	56 ± 24	0.001
SRI-AS (/100)	44 ± 17	53 ± 17	0.012	58 ± 15#	69 ± 17#	0.017
SRI-SR (/100)	64 ± 19	68 ± 22	0.115	75 ± 16	82 ± 16#	0.180
SRI-AX (/100)	43 ± 27	52 ± 26	0.040	47 ± 13	70 ± 23#	0.003
SRI-WB (/100)	50 ± 19	55 ± 19	0.079	62 ± 9#	69 ± 17#	0.020
SRI-SF (/100)	60 ± 22	74 ± 19	0.064	56 ± 22	66 ± 23	0.018
VAS-sleep	35 ± 28	51 ± 23	0.002	40 ± 28	63 ± 26	0.025

	Elective			Acute		
	Baseline (n=33)	**Follow up (n=32)**	p-value	**Baseline (n=17)**	**Follow up (n=14)**	p-value
comfort (/100)						
VAS-activity (/100)	42 ± 24	42 ± 22	0.986	51 ± 18	66 ± 21[#]	0.088
VAS-fatigue (/100)	35 ± 21	50 ± 24	0.003	50 ± 25[#]	72 ± 26[#]	0.046
ESS (/24)	12 ± 6	7 ± 5	<0.001	12 ± 6	5 ± 5	0.001
FSS (/56)	46 ± 14	38 ± 16	0.005	41 ± 15	29 ± 16	0.092

SRI: higher score indicates better quality of life, VAS: higher score indicates greater quality of life; FSS: higher score indicates greater level of fatigue. The table p-value refers to within group change from baseline. [#]independent t-test $p<0.05$ between group difference. Abbreviations: SRI-SS – severe respiratory insufficiency questionnaire summary score, SRI-RC – severe respiratory insufficiency questionnaire respiratory complaints domain, SRI-PF – severe respiratory insufficiency questionnaire physical function domain, SRI-AS – severe respiratory insufficiency questionnaire attendant symptoms and sleep domain, SRI-SR – severe respiratory insufficiency questionnaire social relationships domain, SRI-AX – severe respiratory insufficiency questionnaire anxiety, SRI-WB – severe respiratory insufficiency questionnaire well-being domain, SRI-SF – severe respiratory insufficiency questionnaire social functioning, VAS – visual analogue score, ESS – Epworth sleepiness score, FSS – fatigue severity score.

Ventilator settings showed a higher set IPAP in the fixed level PS arm in the acute (27 ± 3 cmH_2O) compared to the elective (24 ± 2 cmH_2O) group (mean difference 2.8 cmH_2O, 95%CI 0.4 to 5.2 cmH_2O, p=0.025). Set V_{te} was similar in both acute and elective groups in the AVAPS arm. A trend towards increased daily ventilator usage was observed in patients presenting acutely compared with elective presentation (mean difference 73 minutes, 95%CI -8 to 154 minutes, p=0.075) that translated into a significantly higher percentage of days with a ventilator usage of greater than 4 hours (mean difference 25%, 95%CI 7 to 45%, p=0.009). There were no significant between group differences demonstrated in changes in gas exchange, respiratory sleep study parameters or anthropometric measures between baseline and follow up.

4.3: Discussion

This single-blind randomised controlled trial demonstrated that average-volume assured pressure support ventilation has similar efficacy to fixed level pressure support ventilation when accompanied by a strict nurse-led protocolised setup in reducing daytime carbon dioxide level in super-obese patients with OHS. These results are in contrast to previous data suggesting that automated variable pressure support provided enhanced nocturnal ventilatory control, but at a cost of increased sleep disruption. The current data represent the largest randomised controlled trial in super-obese patients with chronic respiratory failure and, as such, these clinical data add to the limited published data available. In addition, these data confirm the findings of previous small studies in less obese patients demonstrating the improvements in daytime gas exchange, daytime somnolence and HRQL that can be achieved with the use of bi-level NIV. In contrast to previous data, this study indicates that nocturnal treatment of chronic respiratory failure in super-obese patients enhances daytime physical activity, which is associated with weight loss.

4.3.1: Critique of method

Study design

The study design used was a single blind randomised controlled trial. The primary outcome was objective and all other assessments were conducted in accordance with international guidelines, when available, or local policies to minimise the chance of assessor bias. This limitation is constant throughout other randomised studies in this area.[92, 160] Although the scientific quality of the current trial would have been enhanced by the addition of a third control arm, the clinical consensus and current evidence strongly support the use of domiciliary NIV in patients with significant nocturnal hypoxia and hypercapnia, such as were enrolled in this study. Survival data from observational studies have demonstrated that in this patient population NIV confers an advantage and therefore we considered that the use of a control arm raised clinical safety and ethical concerns.[153, 166] This is the largest randomised controlled trial in this area and although it was designed with an 80% power there was a lower than expected drop out rate. However the failure to demonstrate treatment superiority of volume targeted PSV may have occurred as a result of a type-2 error.

Limitations of assessment methods

For the purposes of this study, we were focussed on the primary outcome of change in $PaCO_2$ and differences in nocturnal ventilatory control between the volume targeted and fixed level pressure support, assessed and titrated using limited attended respiratory polygraphy. Whilst it is considered ideal to confirm sleep and quantify sleep staging using extended polysomnography, this should not detract from the findings of the trial. Previous studies have shown that oximetry-capnometry is an accurate method to monitor change in $tcCO_2$ in obese patients during NIV initiation.[10, 11, 13, 272] The limitations of extended polysomnography to assess ventilator induced sleep disturbance must also be highlighted. This approach only provides a single night assessment in a monitored hospital setting with a substantial array of electrocephalic, electromyographic and respiratory physiological monitoring equipment attached to the patient, all of which may cause sleep disruption. Notwithstanding the difficulties of assessing the disruptive effects of NIV on sleep, we aimed to investigate the effect of volume targeted and fixed level PS on nocturnal disruption using 7-day actigraphy. As this technique collects data over multiple nights in the home, overcoming the nightly variation occurring with polysomnography,[273, 274] it has also been suggested to be a superior method of assessing treatment associated sleep disruption in OSA.[121] Furthermore, actigraphy has been shown to be a valid method of assessing the sleep-wake cycle in patients with sleep disordered breathing[269, 275] and the previously reported values for total sleep time, wake after sleep onset and sleep efficiency in OHS patients using extended polysomnography are comparable with our current data.[92, 163] Importantly the intra-device reliability of the Actiwatch-64 device is high, allowing useful comparison between patients and time points.[13] Actigraphy has the added benefit of providing objective daytime physical activity data and in the current study it permitted interrogation of the relationships between nocturnal ventilatory control, daytime somnolence, physical activity and weight loss.

4.3.2: Significance of findings

Efficacy of ventilation

Both non-invasive ventilatory modes provided similar control of nocturnal ventilation at baseline and follow up. This was reflected by a similar improvement in hypercapnia at 3 months. These data are in contrast to previous studies demonstrating greater reduction in $tcCO_2$ during volume targeted pressure support ventilation compared to fixed level PS ventilation.[92, 163] However, neither of the previous trials used a study titration protocol, as was used in the current study, to minimise the differences between the groups, and thus the ventilator setup favoured higher levels of pressure support delivered in the volume targeted pressure support ventilation arm resulting in greater carbon dioxide clearance. In addition to previous published data, the data from the current study showed that ≥4 hours nocturnal ventilation was required to achieve a reduction in daytime carbon dioxide. These data are highly relevant to clinicians managing super-obese patients to satisfactory prescribe bi-level NIV.

Effects on sleep disturbance

The present study challenges previous data that showed volume targeted pressure support ventilation contributes to sleep disruption during initiation of NIV in patients with OHS.[163] However, we consider our study design may explain this discrepancy because the previous studies employed a cross-over design, which is methodologically inferior to 1:1 randomisation. Specifically Janssens *et al* randomised their patients in a cross-over design to their 'normal' NIV with or without volume targeted pressure support. Furthermore, the estimated tidal volume was based on the patients' actual body weight (8-10 mL/kg) rather than their ideal body weight, which was the method used in the current study. Not unexpectedly, this study design resulted in a significantly higher mean IPAP in the volume targeted PS group. Therefore, in addition to the unfamiliar mode of ventilation these patients were provided with ventilator settings likely to negatively impact on sleep quality. In contrast, the current study had an *a priori* protocol for titration that produced similar delivered mean PS levels between the groups. The data suggests therefore, that the differences demonstrated in earlier studies were inherent to study design and setup protocol rather than the treatment mode *per se*.

Improvements in health related quality of life and daytime somnolence

Consistent with previous reports, there was a significant treatment effect resulting in improvements in both daytime somnolence and HRQL.[92, 160] There were no differences demonstrated in the magnitude of these improvements between groups, as expected, given that the efficacy of ventilation was similar. Although a larger mean improvement in HRQL occurred in the volume targeted PS treatment arm with more subdomains of the SRI showing within group improvements than in the PS arm. This finding is hypothesis generating and could represent greater improvements in HRQL in the volume targeted PS arm, however, the trial was not powered to detect such differences and to do this would require a substantially larger trial with hundreds of participants that was beyond the scope of this current work.

Improvements in physical activity

As there were no significant differences demonstrated between the intervention groups, we considered that combining them to produce a cohort study is scientifically valid and that this provides useful clinical outcome data determining the effect on nocturnal ventilatory control in a group of super-obese patients with chronic respiratory failure. A reasonable hypothesis has been that there is a direct relationship between enhanced nocturnal ventilatory control and improvement in daytime symptoms which, in turn, has a direct relationship with an increase in daytime physical activity and weight loss. However, evidence for this has been lacking with few studies objectively assessing physical activity following resolution of hypersomnolence in patients with treated sleep-disordered breathing. The most recent data from a randomised controlled trial in male OSA patients with type 2 diabetes compared daytime physical activity using actigraphy in patients who received either therapeutic or sham-CPAP showed no within or between group differences in physical activity levels.[276] Our study population differs from that studied by West *et al* as the patients in the current trial were hypercapnic rather than eucapnic as in the earlier study. Furthermore, half our cohort were female, and the patients in our cohort were substantially more obese. The West *et al* study failed to demonstrate an improvement in physical activity and there was also no weight loss achieved over the duration of the study in the study. This is in contrast to the significant, albeit modest (3%) weight loss in our cohort. Although this level of weight loss

appears minor, weight loss of this magnitude has been shown to be associated with improved metabolic measures in diabetic patients.[277] It cannot be deduced from the data presented whether the changes in activity levels are the cause or effect of the weight loss. However, given the correlation between the changes in activity and changes in anthropometric measures as well as the weight loss comprising of a change in fat mass rather than as the result of resolution of cor pulmonale are supportive of a causal relationship. Given the role of pulmonary rehabilitation in other chronic respiratory disorders this data raises the possibility of augmenting the benefits of treatment in OHS by the addition of specific rehabilitation.[278] The design of future studies of NIV to treat OHS will need to include such measurements.

4.3.3: Ventilatory parameters

Although it is expected that higher levels of pressure support result in greater ventilation, we hypothesised that those patients with lower ventilator triggering rates, and thus a higher proportion of pressure controlled breaths delivered by the ventilator, would have enhanced nocturnal ventilation. We indeed observed that these patients had marked improvements in nocturnal oximetry and capnometry measures, which was reflected in an enhanced improvement in HRQL between initiation and follow up compared to those patients who had higher triggering rates. Apart from a modestly higher $PaCO_2$ in the group more dependent on pressure control ventilation, the groups were reasonably matched at baseline in terms of anthropometrics, spirometry, daytime somnolence and health-related quality of life. As a *post hoc* analysis the conclusions that can be drawn from these data are limited, however the data are hypothesis generating with the greater improvements in both night time and daytime gas exchange and HRQL in patients with greater dependence on back up rate pressure controlled ventilation. This warrants further investigation. It could be postulated that such patients are receiving ventilation that has driven the $PaCO_2$ below their apnoeic threshold and that this would be associated with more rapid re-setting of central respiratory drive and a subsequent improvement in clinical outcomes. This approach could therefore be a more beneficial treatment strategy. Such data informs clinical practice and, in particular, suggests that

clinicians might consider using a spontaneous-timed mode of ventilation in patients with OHS with a moderate back-up rate.

4.3.4: Clinical presentation

Patients with OHS may present both electively via the sleep disorders, bariatric, and respiratory services or acutely following an episode of decompensated episode of acute on chronic respiratory failure. It is acknowledged that OHS is often a missed diagnosis, but it is less clear whether there are inherent demographic and other differences that influence the clinical presentation. Patients were transferred following an acute episode after a period of stabilisation and we observed a lower vital capacity and worse hypercapnic respiratory failure in these patients. An expected consequence of this was higher inspiratory pressures required during NIV set up to establish similar nocturnal oximetry and capnometry control.

Variations in patient self-reported HRQL may, in part, explain the differences between elective and acute clinical presentation of our super obese cohort. Patients presenting electively had greater impairment in terms of self-assessed respiratory complaints, sleep and attendant symptoms, and overall well-being. Patients presenting acutely had correspondingly higher levels, implying that these patients did not perceive the severity of their illness despite having greater physiological derangement at presentation. This lack of correlation between illness perception and physiological impairment is interesting. A rational assumption would be that patients with higher respiratory and sleep symptom burden would be more likely to seek medical attention electively, prompted by their symptoms, and this was reflected in the current data. The variation in illness perception has significant implication to clinical services including emergency and critical care as well as bariatric services as simple symptom screening tools may lack sensitivity and specificity to identify the patients at risk of acute deterioration. It may well be that screening spirometry, clinic oximetry and nocturnal home oximetry will provide greater sensitivity and specificity to screen super obese patients.

4.3.5: Conclusion

These data demonstrate the equivalence of the average-volume assured pressure support mode of NIV compared to standard fixed bi-level NIV in terms of improvements in daytime gas exchange, nocturnal control of sleep disordered breathing, health related quality of life, daytime somnolence and daytime physical activity. The similar degree of sleep disruption occurring between volume targeted PS and fixed bi-level PS refutes previous suggestions of a significant deleterious effect on sleep quality in OHS patients when using this mode of NIV. The data is informative for clinical practice confirming the importance of adherence at the 4 hour level and that improving daytime $PaCO_2$ is an important target for therapy. The data on ventilatory triggering is hypothesis generating implying that improving central respiratory drive may be critical mechanism action of domiciliary NIV in OHS. Finally, the study represents the first attempt to objectively assess daytime activity and its relationship to treatment in this patient group. The results are exciting with the potential to augment the weight loss achieved by NIV with rehabilitation strategies, bridging patients to definitive weight loss procedures.[102]

CHAPTER 5: INTER-OCCASION REPRODUCIBILITY OF A RESPIRATORY PHYSIOLOGICAL BIOMARKER

5.1: Materials and Methods

The background literature of this study can be found on Page 68 of this thesis and the details of patient recruitment was described earlier in this thesis on Page 75.

5.1.1: Baseline data

Following enrolment patients completed the Chronic Respiratory Disease Questionnaire (CRQ), Borg score, modified Medical Research Council (MRC) score, performed handheld spirometry and had respiratory rate, heart rate and oxygen saturations recorded.

5.1.2: EMG_{para} measurement

Patient testing occurred following completion of the pulmonary rehabilitation session at least 30 minutes following last exercise and was repeated at the next session, 3-4 days later. EMG_{para} was acquired and processed as described earlier in the materials and methods section.

5.1.3: Data analysis and statistics

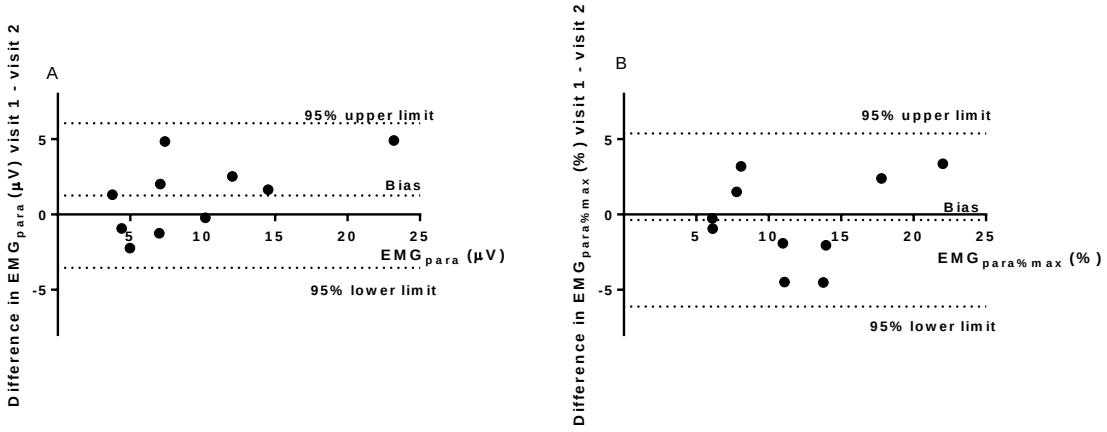
Reproducibility was assessed using Pearson's correlation coefficient, co-efficient of variability and Bland-Altman analysis.[279] Data that were not normally distributed, as defined by the Kolmogorov-Smirnov test, were transformed and then analysed as parametric data or if the logarithm of the data remained non-normal then a non-parametric equivalent was used. Data analysis was conducted using SPSS software (SPSS, Chicago, IL, USA). All data are presented as mean ± SD, unless otherwise stated with a p value <0.05 considered as statistically significant.

5.2: Results

Ten patients with stable COPD were studied with a mean age 75 ± 6.9 years (range 66-85 years), 50% male. Mean FEV_1 was 0.97 ± 0.41 L. The mean EMG_{para} on visit 1 was 8.83 ± 5.29 µV and on visit 2 was 10.09 ± 6.72 µV with a Cv of 0.19 ± 0.13. The mean difference in EMG_{para} was 1.26 ± 2.45 µV

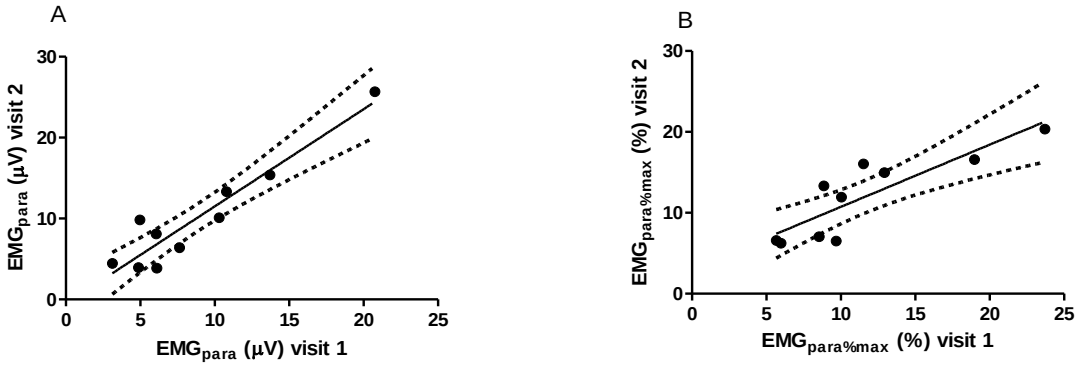
between visits with limits of agreement of -3.54 and 6.06 µV. The mean $EMG_{para\%max}$ value on visit 1 was 11.59 ± 5.70% and on visit 2 was 11.96 ± 5.11% with a Cv of 0.15 ± 0.09. The mean difference in $EMG_{para\%max}$ was -0.37 ± 2.93% between visits with limits of agreement of -6.12 and 5.38%. A Bland-Altman plot of the first and second visit EMG data is provided in Figure 21.

Figure 21: Bland-Altman comparisons for [A] parasternal muscle electromyogram (EMG_{para}) and [B] percent of maxmium parasternal muscle electromyogram ($EMG_{para\%max}$)



Pearson's correlation analysis between visit 1 and visit 2 demonstrated a strong correlation in both EMG_{para} ($r=0.94$; $p<0.001$) and $EMG_{para\%max}$ ($r=0.89$; $p=0.002$), see Figure 22. No significant relationships could be identified between FEV_1 and either EMG_{para} ($p=0.78$) or $EMG_{para\%max}$ ($p=0.46$) or the dyspnoea domain of the CRQ and EMG_{para} ($p=0.17$) or $EMG_{para\%max}$ ($p=0.37$).

Figure 22: Correlation between visit 1 and visit 2 for [A] parasternal muscle electromyogram (EMG_{para}) and [B] percent of maxmium parasternal muscle electromyogram ($EMG_{para\%max}$)



5.3: Discussion

These data demonstrated that the measurement of parasternal electromyography, as a measure of neural respiratory drive, has satisfactory inter-occasion reproducibility in stable patients with COPD. This is a requisite of any test and supports the utilisation of EMG_{para} as a novel respiratory physiological biomarker for measuring changes in the respiratory muscle load-capacity relationship in patients with COPD.

5.3.1: Critique of the method

Patient selection

Stable patients attending pulmonary rehabilitation were chosen as they represented a population of patients that were already both clinically stable and attending hospital on repeat occasions close together. Although possible, it would seem unlikely that the benefit attributable to pulmonary rehabilitation would improve the load-capacity-drive relationship in the short time between the two measurements. Furthermore, this would act to increase the variability and thus the true repeatability may be greater. Again, the use of patients having completed the exercise component of the programme may have some residual breathlessness related to exertion. However, patients were tested following the education session and thus at least 30 minutes following completion of the exercise component of rehabilitation. Borg scores were measured

synchronously with parasternal electromyography and if the Bland-Altman plot was restricted to patients in whom the Borg score was the same on both occasions (n=8), the reproducibility of $EMG_{para\%max}$ was further enhanced with limits of agreement being subsequently narrowed to -3.7% to 5.0%.

Surface EMG_{para} measurement

Although the issues of surface EMG recording are well described,[52] we acknowledge that contamination from other chest wall muscles cannot be excluded. However, we carefully observed patient and electrode position during data acquisition to maximise the contribution of parasternal muscles to the inspiratory EMG_{para} signal and minimising the non-respiratory activity of other muscles. More detailed needle electrode technique could be used to isolate parasternal muscle activity,[217, 280] but similar to oesophageal measurement of diaphragm electrical activity, this invasive technique is not suitable for the acute setting.

Validity and reproducibility of EMG_{para}

EMG_{para}, as a measure of neural respiratory drive, was shown to have satisfactory inter-occasion reproducibility in patients with stable COPD. Although the degree of variability with EMG_{para} in COPD patients was greater in this study than that shown previously by our own group using EMG_{di}[53] and EMG_{para} in patients with cystic fibrosis,[55] the inter-occasion correlation was >0.80, which is a level that has previously been used to indicate acceptable inter-test agreement for surface EMG.[220]

5.3.2: Significance of findings

The data demonstrated that EMG_{para} is a reproducible measure of neural respiratory drive in stable COPD. This provides the requisite support to use EMG_{para} as a novel physiological technique to investigate the load-capacity-drive relationship in the acute setting in COPD.

CHAPTER 6: A RESPIRATORY PHYSIOLOGICAL BIOMARKER TO MONITOR CLINICAL DETERIORATION AND PREDICT READMISSION IN ACUTE EXACERBATIONS OF COPD

6.1: Materials and Methods

The background literature of this study can be found on Page 70 of this thesis. Patient recruitment is as described earlier in this thesis on Page 76. An acute exacerbation of COPD was defined based on clinical features and basic investigations.[201] Initial patient management was according to standard local guidelines with oral corticosteroids, antibiotics and a combination metered-dose inhalers and nebulised bronchodilators. Patients were identified by the COPD team and subsequently screened and recruited by the research team, with the first EMG_{para} measurement recorded within 24 hours of hospital arrival. Repeat EMG_{para} measurements and the clinical dataset were recorded daily until the patient was reported as stable and suitable for hospital discharge.

6.1.1: Baseline data

Demographic and anthropometric data were collected at patient recruitment. Borg score[281] and MRC dyspnoea score[282, 283] were used to assess subjective breathlessness. HRQL data was obtained using the CRQ.[88] Spirometry was performed with a handheld device (EasyOne Diagnostic Spirometer, ndd Medical Technologies, Switzerland) according to standard guidelines.[284, 285] Repeat measurements were taken daily during admission until patient was either discharged or deemed medically fit for discharge. The patient was positioned comfortably and rested for at least 5 minutes; bronchodilator therapy was withheld for the previous 4 hours. Heart rate (HR), oxygen saturations (S_pO_2) and respiratory rate (RR) were measured over one minute. Clinical data (HR, S_pO_2, RR, temperature, blood pressure and Medical Early Warning score (MEWS)[286]) and the supervising senior clinician's summary opinion on clinical course were recorded from the medical notes and observation charts. A patient was defined as a clinical 'deteriorator' or 'improver' based on the summary opinion of the senior attending respiratory physician (respiratory specialist registrar or consultant) and the requirement for increased treatment. The respiratory clinicians were blinded to the EMG_{para} measurement, which was

analysed off line following patient discharge. EMG_{para} signals were acquired either in a chair or semi-recumbent in bed. Oxygen therapy was only used when the S_pO_2 was ≤ 88%.

6.1.2: EMG_{para} measurements

Signal acquisition was performed as described in the materials and methods section of this thesis on Page 86. The resting signal was normalised to the maximum value obtained from a reproducible maximum sniff manoeuvre to produce the $EMG_{para\%max}$. To reflect changes in respiratory pattern, the product of $EMG_{para\%max}$ and respiratory rate was calculated to produce the neural respiratory drive index (NRDI; arbitrary units AU). Nasal cannulae connected to a differential pressure transducer (Validyne DP45, Validyne, Northridge, CA, US) identified inspiratory and expiratory phases of breathing. In addition to EMG_{para} EMG signals were acquired from the right sternocleiodomastoid muscle and right internal oblique abdominal muscle.

6.1.3: Data analysis and statistics

Relationships between $EMG_{para,}$ $EMG_{para\%max}$ and NRDI and lung function parameters and HRQL data were analysed using regression analysis. Data were analysed using independent or paired t-test where appropriate. Data that were not normally distributed, as defined by the Kolmogorov-Smirnov test, were transformed and then analysed as parametric data or if the logarithm of the data remained non-normal then a non-parametric equivalent was used. Data analysis was conducted using SPSS software (SPSS, Chicago, IL, USA). All data are presented as mean ± SD or median (range), unless otherwise stated with a p-value <0.05 considered as statistically significant.

6.2: Results

6.2.1: Change in EMG_{para} in patients with acute exacerbations of COPD

30 patients were recruited with a mean age of 72 ± 10 years (47% male). On admission, the median MRC dyspnoea score was 5 (2-5). The median previous admission frequency and length of stay was 3 admissions (0-13) and 6 days (2-34), respectively. Baseline data are provided in Table 21 and Table 22. 3 patients received non-invasive ventilation with all cases initiated in the first 4

hours of admission in the emergency department. 9 patients were discharged with home oxygen, all were previously prescribed long term oxygen therapy.

Table 21: Individual baseline admission data for patients admitted with an acute exacerbation of Chronic Obstructive Pulmonary Disease

	Age (years)	Sex (M/F)	EMG_{para} (μV)	$EMG_{para\%max}$ (%)	NRDI (AU)	MEWS	Borg	RR (bpm)	FEV_1 (L)
1	64	F	12.6	9.1	238	3	4	26	UTP
2	73	F	8.4	12.9	271	2	1	21	0.32
3	57	M	40.0	25.0	799	3	4	32	UTP
4	70	F	43.1	52.1	1512	4	7	29	0.52
5	72	M	7.5	11.0	221	1	3	20	1.64
6	72	F	5.8	21.0	543	3	6	26	UTP
7	77	M	3.7	11.5	298	2	7	26	0.49
8	81	F	14.0	21.2	509	2	6	24	0.46
9	68	F	22.4	20.3	406	1	4	20	UTP
10	64	M	16.8	25.3	506	1	7	20	0.69
11	80	F	6.5	13.9	291	4	3	21	0.58
12	74	F	9.2	14.8	355	2	2	24	0.45
13	69	F	18.6	16.0	383	2	8	24	0.49
14	89	F	21.8	36.7	808	2	1	22	0.24
15	90	M	8.3	14.0	252	1	0.5	18	0.69
16	79	M	6.4	16.9	422	3	5	25	0.48
17	85	F	7.5	16.2	390	3	7	24	0.53
18	72	F	16.4	10.4	249	2	4	24	UTP
19	72	F	9.5	12.2	231	1	5	19	0.62
20	75	F	19.8	15.7	378	4	8	24	0.44
21	63	F	18.4	28.1	534	1	8	19	0.60
22	72	M	20.9	32.3	550	1	3	17	0.67
23	75	F	16.3	36.7	770	3	4	21	0.34
24	83	M	15.7	17.9	287	0	0	16	1.58
25	43	M	13.3	21.0	440	2	3	21	0.50
26	64	M	17.4	25.1	527	2	9	21	0.45
27	62	M	16.7	29.7	594	2	3	20	0.58

	Age (years)	Sex (M/F)	EMG_{para} (μV)	$EMG_{para\%max}$ (%)	NRDI (AU)	MEWS	Borg	RR (bpm)	FEV_1 (L)
28	85	M	6.2	13.2	304	2	3	23	0.82
29	63	M	3.0	8.0	144	1	5	18	2.11
30	80	M	10.5	21.3	426	1	9	20	0.96
Mean ± SD	72 ± 10		14.6 ± 9.3	20.32 ± 9.85	455 ± 263	2 (0-4)*	4 (0-9)*	22 ± 4	0.60 ± 1.65

Abbreviations: EMG_{para} – Parasternal muscle electromyogram, $EMG_{para\%max}$ – percentage of maximum obtainable parasternal muscle electromyogram, NRDI – neural respiratory drive index, MEWS – medical early warning score, RR – respiratory rate, FEV_1 – forced expiratory volume in 1s, UTP – patient unable to perform.

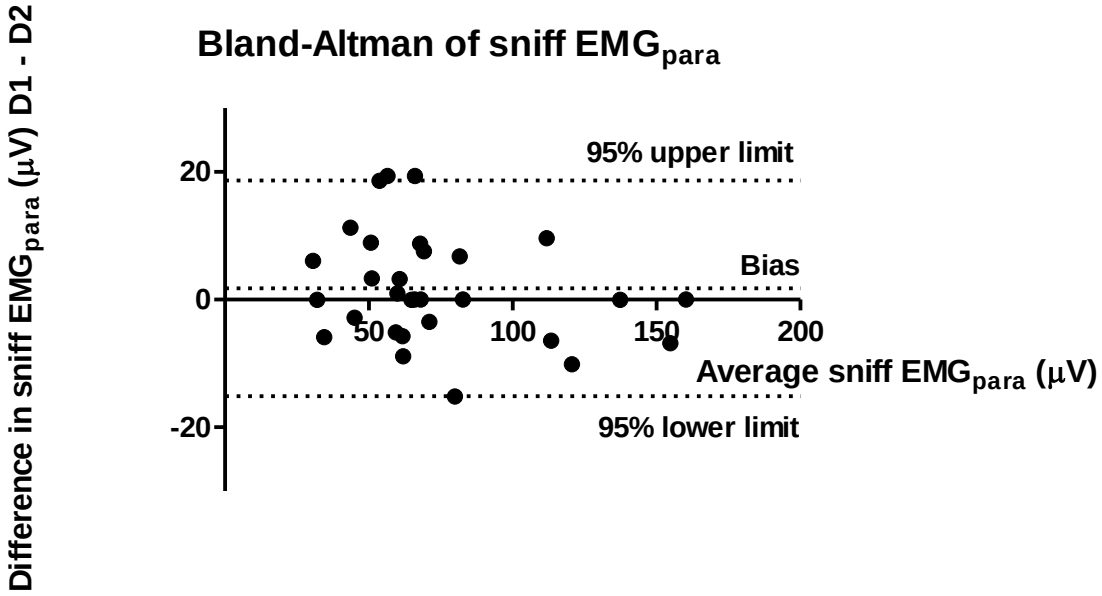
Table 22: Summary of clinical parameters and indices of neural respiratory drive on admission

	Emergency department	Baseline measurements
MEWS	3 (0-7)	2 (0-4)
FEV_1 (L)	-	0.60 ± 1.65
FVC (L)	-	1.53 ± 0.82
P_aO_2 (kPa)	10.0 ± 3.5	-
P_aCO_2 (kPa)	6.3 ± 1.4	-
$EMG_{para\%max}$ (%)	-	20.3 ± 9.9
NRDI (AU)	-	455 ± 263

Abbreviations: MEWS – medical early warning score, FEV_1 – forced expiratory volume in 1s, FVC – forced vital capacity, PaO_2 – arterial partial pressure of oxygen, $PaCO_2$ – arterial partial pressure of carbon dioxide, $EMG_{para\%max}$ – percentage of maximum obtainable parasternal muscle electromyogram, NRDI – neural respiratory drive index.

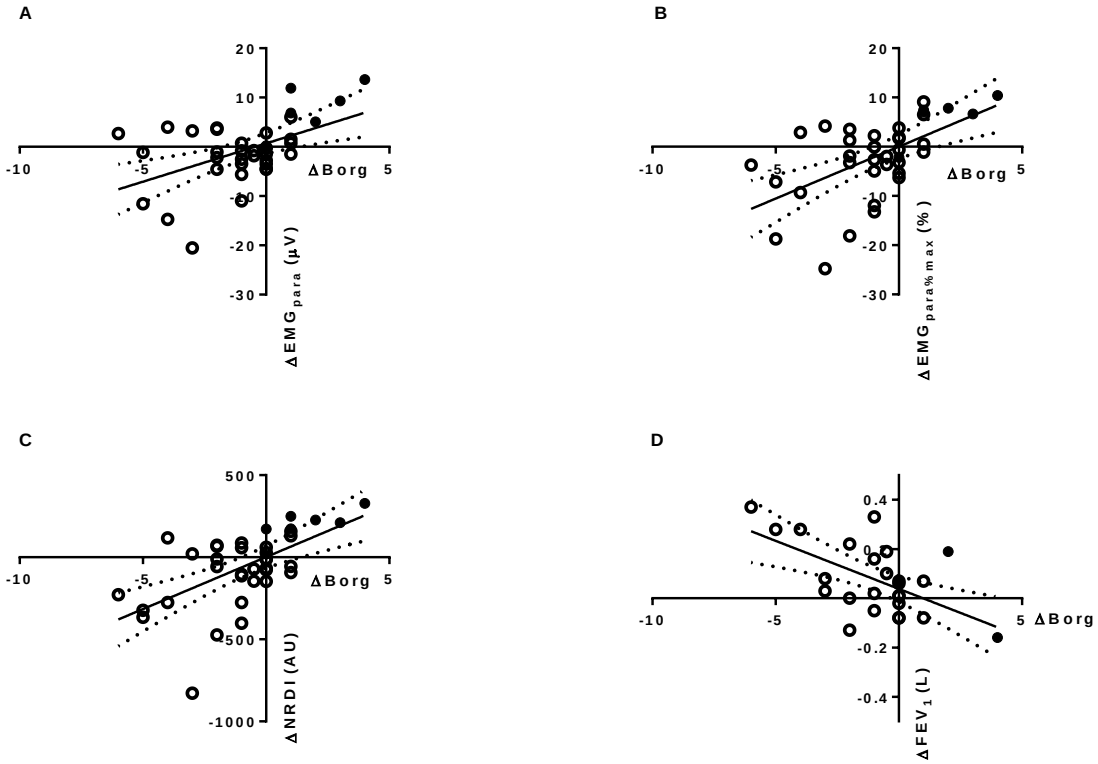
24 patients had recordings on 2 occasions, 5 patients had recordings on 3 occasions and 1 patient had recordings on 4 occasions, producing 37 data pairs. The daily values for sniff EMG_{para} were highly correlated ($r=0.97$, $p<0.001$) with minimal bias (Figure 23).

Figure 23: Daily repeatability of maximum sniff parasternal muscle electromyogram (EMG_{para})



ΔBorg score had a significant relationship with ΔEMG_{para} (r=0.50; p=0.001), $\Delta EMG_{para\%max}$ (r=0.57; p<0.001) and ΔNRDI (r=0.60; p<0.001) and ΔFEV_1 (r=-0.58; p=0.002) as shown in Figure 24. There was no relationship observed with ΔS_pO_2 (p=0.16) or ΔRR (p=0.08). The indices of neural respiratory drive also correlated with changes in respiratory rate. A non-significant trend was demonstrated in the relationship between ΔFEV_1 and $\Delta EMG_{para\%max}$ (p=0.053) and ΔNRDI (p=0.057). There were no significant changes demonstrated in the standard physiological parameters in 'deteriorators' between repeat assessments, but there were significant increases in the indices of neural respiratory drive (mean difference $EMG_{para\%max}$=6.2, 95%CI 1.7 to 10.7, p=0.017; mean difference NRDI=226, 95%CI 165 to 288, p<0.001) and a non-significant increase in MEWS (p=0.07) between occasions.

Figure 24: Comparison of change in Borg score with change in [A] parasternal muscle electromyogram (EMG_{para}), [B] percent of maxmium parasternal muscle electromyogram ($EMG_{para\%max}$), [C] Neural respiratory drive index (NRDI) and [D] Forced expiratory volume in 1s (FEV_1)*



Showing data from 37 pairs of readings generated from consecutive recordings of physiological variables in 30 patients. Open circles represent 'improvers' and closed circles 'deteriorators'. *data from 26 pairs of data.

Baseline $EMG_{sc\%max}$ was 13.4±8.5% with no statistically significant changes occurring during the first 24 hours of admission in either improvers or deteriorators. There were no significant relationships between $EMG_{sc\%max}$ and other markers of NRD, measures of dyspnoea, spirometric measures or in the standard clinical variables.

There were significant differences observed in mean change between 'improvers' and 'deteriorators' in all three EMG_{para} indices. However, there were no significant between group differences in changes in RR, HR, S_pO_2 or FEV_1 (Table 23). A significant (p=0.02), but clinically small (0.5), difference was observed in MEWS between 'improvers' and 'deteriorators'. Patients who improved had statistically significant reduction in dyspnoea (ΔBorg -1.5; 95%CI

-0.7 to -2.3, p=0.001), respiratory rate (ΔRR -1.8bpm; 95%CI -0.2 to -3.3, p=0.027) and increase in FVC (ΔFVC 0.22 L; 95%CI 0.05 to 0.40, p=0.013), with no statistically significant differences demonstrable in physiological variables in the 'deteriorators'.

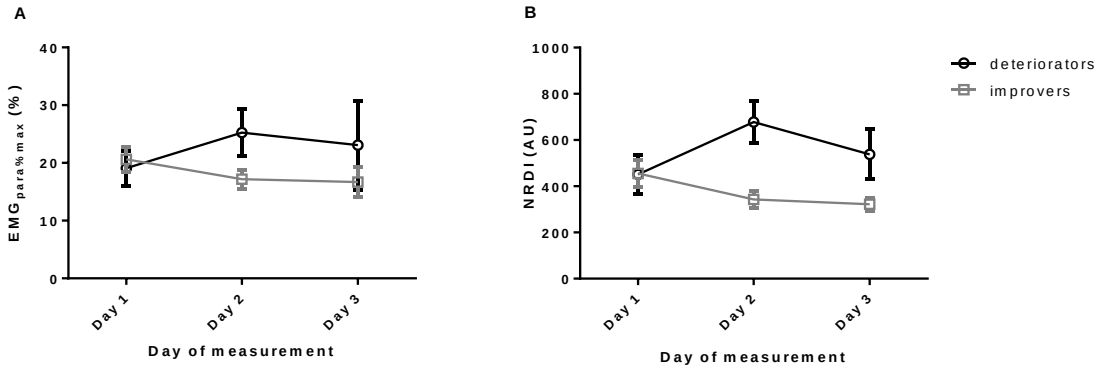
Table 23: Difference between consecutive recordings of measured physiological variables in 30 patients from day of baseline measurement to repeat reading

	'Deteriorators'	**'Improvers'**	Mean difference (95%CI)	p-value
ΔMEWS	0.50 (0 - 1)	0 (-2 - 1)		0.019
ΔRR	4.5 ± 6.0	-1.8 ± 3.8	6.3 (-0.1 to 12.6)	0.051
ΔS_pO_2	1.2 ± 2.4	0.9 ± 2.7	-0.3 (-2.3 to 2.8)	0.829
ΔFEV_1*	0.03 ± 0.18	0.06 ± 0.14	0.03 (-0.42 to 0.36)	0.786
ΔEMG_{para}	7.8 ± 4.9	-1.7 ± 5.5	9.6 (4.4 to 14.8)	0.003
$\Delta EMG_{para\%max}$	6.2 ± 4.3	-3.5 ± 8.1	9.6 (4.5 to 14.8)	0.001
ΔNRDI	226 ± 58	-113 ± 221	339 (234 to 444)	<0.001

*7 patients were unable to perform spirometry on 1 or more occasions, therefore analysis of FEV_1 was performed on 'improvers' n=20 and 'deteriorators' n=3. Abbreviations: MEWS – medical early warning score, RR – respiratory rate, SpO_2 – oxyhaemaglobin saturation, FEV_1 – forced expiratory volume in 1s, EMG_{para} – Parasternal muscle electromyogram, $EMG_{para\%max}$ – percentage of maximum obtainable parasternal muscle electromyogram, NRDI – neural respiratory drive index.

Both 'improvers' and 'deteriorators' had similar levels of NRD at initial reading that were significantly different at the follow up reading 24 hours later (mean difference $EMG_{para\%max}$=8.1, 95%CI 0.2 to 16.0, p=0.046; mean difference NRDI=335, 95%CI 163 to 507, p<0.001). Significant differences in NRD did not persist in subsequent measurements (Figure 25).

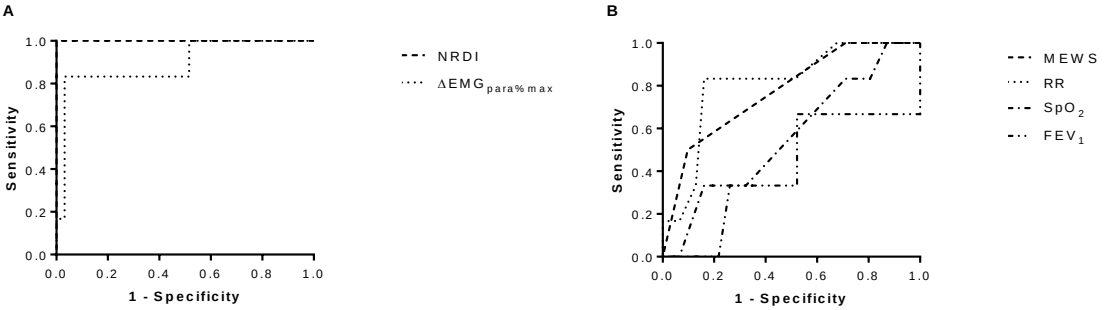
Figure 25: Daily changes in [A] percent of maxmium parasternal muscle electromyogram ($EMG_{para\%max}$) and [B] neural respiratory drive index (NRDI) during the course of admission between patients designated as 'improvers' or 'deteriorators' during the first 24 hours of study participation



Plotted as mean ± standard error of the mean.

Receiver operating characteristics (ROC) plots (Figure 26) with change 'cut offs' >+6.6 for $EMG_{para\%max}$ and >+160AU for NRDI had sensitivities of 83% (95%CI 54 to 100%) and 100% (95%CI 100 to 100%) and specificities of 96% (95%CI 88 to 100%) and 100% (95%CI 100 to 100%) for both $EMG_{para\%max}$ and NRDI, respectively. ROC plots of the standard clinical variables either did not statistically differ from the null hypothesis or could not produce a 'cut off' providing sensitivity >80% without reducing specificity to <90% (Figure 26). The best performing routine physiological variable was respiratory rate that provided a sensitivity of 83% (95%CI 54 to 100%) and a specificity of 88% (95%CI 74 to 100%) to detect clinical deterioration using a cut off of an increase in respiratory rate of 2 breaths per minute.

Figure 26: Receiver Operating Characteristic (ROC) plot of change in [A] percent of maxmium parasternal muscle electromyogram ($EMG_{para\%max}$) and neural respiratory drive index (NRDI) and [B] respiratory rate (RR), medical early warning score (MEWS), oxyhaemoglobin saturation (SpO_2) and forced expiratory volume in 1s (FEV_1) for detection of clinical deterioration



6.2.2: Change in EMG_{para} between admission and discharge to predict readmission

A significant difference in ΔEMG_{para} and ΔNRDI between admission (1st measurement within 24 hours of admission) and discharge (final measurement within 24 hours of clinical stability) was demonstrated between those patients readmitted within 14 days as a consequence of a respiratory deterioration and those patients who remained at home. However, ΔMEWS, ΔFEV_1 and number of previous admissions did not differ between patients who were and were not readmitted (Table 24).

Table 24: Difference between admission and discharge of measured physiological variables in 30 patients either readmitted (n=9) or not readmitted (n=21) within 14 days of hospital discharge

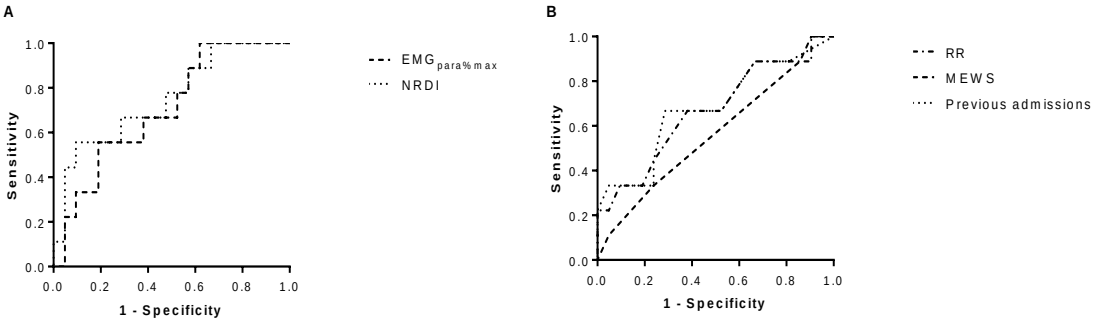
	Readmitted	**Not readmitted**	Mean difference (95%CI)	p-value
ΔMEWS*	0 (-1 - 2)	0 (-3 - 2)		0.5
ΔFEV_1*	0.09 ± 0.15	0.08 ± 0.10	0.1 (0.14 to 0.11)	0.8
Previous admissions*	4 (0 - 14)	3 (0 - 10)		0.1
$\Delta EMG_{para\%max}$	1.98 ± 4.36	-4.05 ± 10.30	6.03 (11.5 to 0.54)	0.03

	Readmitted	Not readmitted	Mean difference (95%CI)	p-value
∆NRDI	76 ± 134	-127 ± 305	203 (39 to 366)	0.02

*7 patients were unable to perform spirometry on 2 occasions, therefore analysis of FEV_1 was performed on readmitted n=6, not readmitted n=17. Abbreviations: MEWS – medical early warning score, FEV_1 – forced expiratory volume in 1s, $EMG_{para\%max}$– percentage of maximum obtainable parasternal muscle electromyogram, NRDI – neural respiratory drive index.

ROC plots (Figure 27) were calculated with 'cut offs' of a change in $EMG_{para\%max}$ >0% and NRDI >50AU during admission producing sensitivities of 67% (95%CI 36 to 97%) and 67% (95%CI 36 to 97%) and specificities of 62% (95%CI 41 to 83%) and 71% (95%CI 52 to 91%) for $EMG_{para\%max}$ and NRDI, respectively. None of the ROC plots for routine clinical variables differed significantly from the null hypothesis (Figure 27).

Figure 27: Receiver Operating Characteristic (ROC) plot of change in in [A] percent of maxmium parasternal muscle electromyogram ($EMG_{para\%max}$) and neural respiratory drive index (NRDI) and [B] respiratory rate (RR), medical early warning score (MEWS) and number of previous admission for hospital readmission at 14 days



6.3: Discussion

This study has demonstrated that 2nd intercostal space parasternal neural respiratory drive index, calculated as a product of EMG_{para} and RR normalised for maximum EMG_{para}, is a reproducible physiological biomarker in stable COPD patients and has greater sensitivity and specificity than standard clinical physiological parameters to identify patients failing to respond to treatment for acute exacerbations of COPD. Furthermore, the failure of NRDI to fall during

an exacerbation requiring hospitalisation identifies patients who are more likely to be readmitted with a further respiratory deterioration.

6.3.1: Critique of the method

Patient selection

The patients recruited were not consecutive admissions and therefore subject to selection bias. Despite this limitation, demographics and severity of patients were similar to previously reported data.[208] Furthermore, the goal of this study was to provide pilot data to demonstrate the feasibility and clinical usefulness of using non-invasive EMG monitoring as a physiological biomarker in the acute setting. Although the cohort only had a moderate severity of illness, based on the median MEWS, it must be realised that this is a scoring system that is only validated in general medical patients.[286] MEWS has never been validated in a COPD acute exacerbation cohort and even in the general medical patients the area under the curve of the ROC curve is <0.7. MEWS reports cardiovascular and respiratory clinical instability with cerebral function and thermal dysregulation. During an acute exacerbation of COPD, patients are unlikely to have instability of blood pressure, cerebral dysfunction or thermal dysregulation and any patient who was not able to consent (e.g. impaired cognition) was excluded from this study. MEWS is not considered as either a specific or sensitive test for estimating the exacerbation severity or monitoring patients with acute exacerbation of COPD. The patients in this study had similar exacerbation severity to that of the British Thoracic Society National Audit as regards age, although the cohort in the current study had marginally greater airflow obstruction and levels of dyspnoea, as measured by MRC score.[287] The patient population in this study can reasonably be assumed to be representative of patients admitted to UK hospitals.

Surface EMG_{para} measurement

Generic issues regarding surface EMG_{para} measurement are discussed in the Chapter Inter-occasion reproducibility of a respiratory physiological biomarker, section 5.3.1: Critique of the method, page 124. Specifically, during the current study we further evaluated the repeatability of the sniff manoeuvre. It was expected that tidal EMG_{para} values would change in response to treatment but that sniff EMG_{para} as a maximal manoeuvre would not show pronounced daily

variability. As would be expected from a maximal manoeuvre in the context of an acute exacerbation, the limits of agreement are relatively wide. This may, in part, be due to the variability in placement, as opposed to true changes in muscle activation due to any volitional variation on a daily basis. There is no systematic bias in terms of signal intensity or day-to-day variation in sniff EMG_{para}, and therefore this should not detract from the clinical usefulness of this test.

Validity of surface EMG

The protocol for the study concentrated on parasternal surface EMG whereas it can be argued that for an accurate assessment of respiratory muscle activity to be made the measurement of electrical activity of the diaphragm and extra-diaphragmatic accessory respiratory muscles, such as sternocleidomastoid muscle should be obtained. As part of this study, assessment of sternocleidomastoid muscle activity was achieved in a subset of patients. However, in contrast to the diaphragm and 2nd intercostal space parasternal muscle, which are primarily respiratory muscles, sternocleidomastoid has both respiratory and non-respiratory function (e.g. rotational movement of the head) and consequently the non-respiratory activity interfered with respiratory activity of sternocleidomastoid preventing accurate and reliable measurements.

The study took place with support from an established research group with extensive experience of measuring diaphragm EMG activity using the oesophageal electrode.[53] This technique has been shown to be significantly superior to surface EMG measurement of diaphragm activity. However, the invasive technique of measuring diaphragm EMG was considered inappropriate in patients experiencing an exacerbation of COPD. Such patients have high levels of dyspnoea and anxiety and passing an oesophageal electrode would not be possible in routine clinical practice and therefore this would significantly limit the usefulness of neural respiratory drive as a physiological biomarker and novel clinical assessment tool.

The use of surface EMG_{di} is more suited to investigations of healthy subjects and stable COPD patients during resting breathing because of the crosstalk between muscles contaminating surface diaphragm EMG measurements and

variation in skin surface impedance.[52] With recruitment of the abdominal muscles, during exercise or acute exacerbation, the surface EMG_{di} signal becomes contaminated, reducing the usefulness of this technique. Furthermore, there is no standard for position of surface electrodes for measurement of EMG_{di} or readily identifiable landmarks to assist interoccasion reproducibility. In contrast the measurement of EMG_{para} is assisted by easily identifiable surface landmarks facilitating its use as a respiratory physiological biomarker. There is no clear consensus for the positioning of surface diaphragm electrodes making comparison between studies difficult. In addition, the surface landmarks for electrode placement are often difficult to locate thus making reproducibility poor and failing to minimise the contribution of the nearby abdominal muscles, which are often active in severe COPD, especially during an exacerbation when flow limitation is at its peak.[51, 288, 289] Surface diaphragm EMG measures costal as opposed to crural diaphragm activity and whilst the two parts of the diaphragm appear to have similar activation and activity it is by no means clear that costal diaphragm EMG represents overall diaphragm activity during all activities.[52] For the reasons stated above, the 2nd intercostal space parasternal muscle was used in this study as the principal component of NRD, reflecting its attributes as a respiratory muscle with similar activity to the diaphragm with easily identifiable landmarks and minimal cross-talk with other muscles.

Definition of clinical change

The lack of an objective measure to monitor clinical progress in the acute setting to allow comparative changes with EMG_{para} is an obvious limitation of this study. All patients met an event based criteria for a severe exacerbation of COPD requiring hospital admission.[290, 291] It is acknowledged that there is no 'gold standard' to predict or measure acute clinical progress in an exacerbation of COPD,[291] and therefore we compared EMG_{para} to standard clinical parameters and the summary opinion of the supervising senior physician. Whilst this is a broad definition it is widely used in both research and clinical practice and is the benchmark by which other novel influential assessment tools have been judged.[292] In validating the EXACT tool Leidy *et al* [292] used physician rated exacerbation severity and physician judged treatment response

to act as the benchmark comparators i.e. physician's clinical judgment was treated as the 'gold standard'. We, therefore, consider that despite the possible subjective nature of the definition of 'improvers' and 'deteriorators', this assessment genuinely represents the 'gold standard' to which this novel assessment tool of neural respiratory drive could effectively be judged. In the current study, the physician judged treatment response was reported by the most senior clinician (Respiratory Consultant or Respiratory Specialist Registrar) reviewing the patient on that day and represents the summary assessment of the attending team, consisting of the junior medical team, nurses and specialist physiotherapists. Clinical gestalt is the interpretation by physicians of the patient's report of their clinical state as well as examination incorporating standard physiological variables and clinical parameters, which are subsequently processed as part of learnt complex clinical algorithm. This is a robust clinical assessment tool and an adequate comparator. Criteria to define 'improvers' and 'deteriorators' were not provided in this study as there is no clear consensus on a method to which this could be sufficiently defined. The authors consider that providing set criteria, either based on patient symptom scores, physiological criteria or treatment changes, may interfere with the attending clinician assimilating the available information to produce a clinical summary opinion and would give an arbitrary, poorly understood and non-validated method of defining treatment success. In this study, patients admitted with an acute exacerbation of COPD were managed by respiratory specialist who would be expected to be able to produce a valid clinical assessment on patient response to treatment.

Although there was no significant difference in specific physiological markers between 'improvers' and 'deteriorators', the trends were in the expected direction. The 'improvers' had statistically significant reduction in dyspnoea, respiratory rate and increase in FEV_1 that support the physicians' clinical judgment of treatment response. This is also supported by the observation that there were no significant improvements in any physiological variables in the 'deteriorators' group.

Despite the limitations inherent with this choice of outcome it allows the data to be easily interpreted. In order to have measured the performance of this novel

technique against a more definable objective marker the study population may have to be limited to those patients in hypercapnic respiratory failure. Such patients admitted directly to intensive care unit with severe respiratory failure were excluded from this study. These patients were excluded as they represent a separate population from the cohort of patients recruited for this study. 3/30 (10%) patients of the cohort received NIV as part of their acute exacerbation management, similar to previous published data.[208] All these patients received NIV from admission and there were no patients that deteriorated sufficiently, following admission to the respiratory ward, to require initiation of NIV. These data are consistent with published data that only 1 in 20 patients develop respiratory acidosis following admission.[208] Had the study population been restricted to those with decompensated respiratory failure it would have limited the applicability of the study and it would have been difficult to demonstrate that measures of NRD added to already established and widely available techniques to measure clinical progress in this group.

6.3.2: Significance of findings

Dyspnoea

Dyspnoea provides a significant symptom burden in COPD with its importance as a marker of disease severity recently noted by its incorporation into the GOLD guidelines.[270] An objective method of assessing the severity of breathlessness has previously been lacking, with clinicians using subjective assessment tools. Physiological indicators of disease severity in COPD, such as FEV_1, are acknowledged to be poorly predictive of dyspnoea.[293] In contrast, changes in NRD have been shown to explain variance in exercise induced dyspnoea.[243] In the current study, we observed a similar relationship between change in Borg score and change in EMG_{para}. The initial measurements were recorded following initiation of emergency therapy, and in some patients there were relatively small changes in 2nd intercostal space parasternal muscle electrical activity and breathlessness, indicating that that the technique is sensitive enough to monitor relatively modest changes even after treatment initiation. These data, therefore, support the use of non-invasive EMG_{para} as a physiological biomarker of NRD that reflects perception of dyspnoea severity during COPD exacerbations. Furthermore, as FEV_1 has a weak relationship

with dyspnoea, there is potential for EMG_{para} to be applied to patients in the stable state to monitor progression of disease and detect exacerbation onset, although more work is required to fully elucidate this relationship.

Monitoring response to treatment

NRD was shown to monitor response to treatment in patients admitted with acute exacerbations of COPD when calculated as $EMG_{para\%max}$ and NRDI. The reproducibility data indicates that the 'cut off' chosen for maximum sensitivity and specificity of detection of clinical change ($EMG_{para\%max}$ >6.6%) represents a genuine and detectable change in NRD as it is above the 95% upper limit of agreement on the Bland-Altman plot for inter-occasion variabilty. In this population of patients, this would have correctly tracked deterioration in 5 out of 6 occasions. This high sensitivity and specificity can be further improved with the addition of respiratory rate to produce the NRDI, which correctly identified all episodes of deterioration in this sample set. This demonstrates the potential clinical utility of the test with the integrated physiological signal accurately reflecting the summary opinion of the senior attending respiratory physician in a way unable to be replicated by any of the standard clinical variables assessed.

Re-admission

In addition to the ability to track changes in NRD during acute exacerbations using this technique, the failure of NRD to fall in response to therapy identifies those patients who were likely to be readmitted within 14 days of discharge due to a further respiratory deterioration. Whilst some biomarkers have allowed identification of COPD phenotypes during the stable state and that these can predict behaviour at the time of exacerbation[294] there remains few clinically useful biomarkers that can predict readmission in these patients.[295] Previous data has indicated that COPD patients with severe disease, as indicated by an FEV_1 <1 L at discharge or >2 previous admissions in the preceding 12 months, reported that these patients were more likely to be readmitted following an exacerbation of COPD than those with less severe disease.[296] The specificity of these particular predictors in the current cohort of patients was poor at <0.5 and therefore these are not clinically useful. Failure of NRD to fall in response to treatment provides an easy to apply novel physiological biomarker to predict readmission in high risk patients. Data from the ECLIPSE study has suggested

the 'frequent exacerbator' is a distinct phenotype in COPD.[297] The measurement of NRD in this context is not simply acting as a measure of disease severity or to identify the frequent exacerbator phenotype; if our analysis were limited to those patients with ≥2 previous admissions (n=22), the sensitivity and specificity to predict readmission at 14 days remained similar to the whole cohort at 63% and 64%, respectively. The ability of this physiological tool to maintain its sensitivity and specificity in the higher risk group of patients increases its clinical utility, with the ability to further risk stratify the most high risk patients. With the increasing role of early discharge and COPD outreach schemes to support patients in the community,[198, 199] this technique could facilitate clinical selection to identify those patients that require greater community support or further hospital treatment prior to discharge. This approach has increasing importance as the rising incidence of failed hospital discharge have been highlighted by the Department of Health as an area for improved performance.[198] Although these observational data have demonstrated that measures of NRD can identify treatment failure and re-admission risk in patients with acute exacerbations of COPD further validation of the technique is required with prospective interventional trials. These could focus on the ability to identify treatment failure to allow patients to be discharged with standard or supportive care packages with the aim of reducing readmissions and the serious sequelae of repeated exacerbations.

6.3.3: Conclusion

Neural respiratory drive, measured from 2nd ICS parasternal electromyography, is an objective physiological biomarker in COPD patients hospitalised with acute exacerbations. The technique is well tolerated and feasible in the acute care setting. More importantly neural respiratory drive, in contrast to other standard clinical parameters, is able to provide an objective marker of dyspnoea, track the clinical state of patient during an exacerbation of COPD and predict risk of readmission at 14 days.

CHAPTER 7: PHYSIOLOGICAL SUB-STUDY OF THE HOME OXYGEN THERAPY VS. HOME MECHANICAL VENTILATION IN PATIENTS WITH PERSISTENT HYPERCAPNIA POST EXACERBATION OF COPD TRIAL (HOT-HMV UK TRIAL)

7.1: Materials and Methods

The background literature of this study can be found on Page 70 of this thesis. Patient recruitment is described earlier in this thesis on Page 76. All subjects provided written informed consent prior to enrolment. The study was approved by St Thomas' Hospital Research Ethics Committee (09/H0802/2) and performed in line with local governance procedures (RJI 09/N070). The study was registered prospectively on a publically accessible database (NCT00990132).

7.1.1: Subjects

Patients referred to the Lane Fox Respiratory Unit, St Thomas' Hospital and the Sleep & Ventilation Unit, the Royal Brompton Hospital for consideration of domiciliary non-invasive ventilation (NIV) were screened for trial eligibility.

7.1.2: Study design

An open labelled randomised controlled design study was used. Randomisation was conducted independently of the study group at the Oxford Respiratory Clinical Trials Unit using minimisation.

Minimisation variables were:

- Age (<65 years/ ≥65 years), BMI (≤20 kgm^{-2}/ >20 kgm^{-2})
- Prior use of long term oxygen therapy (yes/no)
- Number of previous COPD related admissions in the last 12 months (<3, ≥3).

7.1.3: Study intervention

HOT and HMV were setup as described earlier in this thesis on page 92.

7.1.4: Study measurements

Patients underwent baseline assessment of anthropometrics including fat free mass measured by bioelectrical impedance analysis using a validated disease

specific regression algorithm.[251] Pulmonary function tests including spirometry, static lung volumes, gas transfer and reversibility were performed according to international guidelines.[264, 298] Health related quality of life questionnaires including SRI, SGRQ and ESS were completed. Arterial blood gas analysis was performed with the patient in a seated position whilst breathing room air for 20 minutes at least 4 hours after waking. Patients underwent diagnostic limited respiratory polygraphy on either oxygen therapy or room air depending on result of daytime ABG. Patients with severe resting hypoxaemia (PaO_2 <7.3 kPa) were treated with nocturnal oxygen therapy and those with moderate hypoxaemia (PaO_2 7.3-8 kPa) had the diagnostic respiratory sleep study performed on air to assess for nocturnal hypoxia and thus indication for HOT. A subsequent oximetry-capnometry study was performed on an oxygen flow rate at the prescribed level. Patients then had an early morning ABG performed to assess for respiratory acidosis on oxygen therapy. A repeat oximetry-capnometry was performed on the patients randomised to HMV.

Pulmonary physiology

Patients underwent full invasive pulmonary physiological testing, as described earlier in the Materials and Methods section on Page 80, including measurement of respiratory muscle strength, dynamic intrinsic positive end expiratory pressure ($_{dyn}PEEP_i$), dynamic lung compliance (C_{dyn}), tidal breathing, neural respiratory drive (EMG_{para}, EMG_{di}, EMG_{sc} and EMG_{abdo}) and hypercapnic responsiveness testing using the rebreathe technique.[234]

7.1.5: Follow up

Patients underwent follow up assessment at 6 weeks, 3 months, and 6 months. The study plan with details of all the assessments performed at each visit is provided in Table 25.

Table 25: Study plan for HOT-HMV UK trial

	Baseline	Follow up		
		6 weeks	3 months	6 months
Randomisation	**X**			
Treatment Standardization	**X**			

	Baseline	Follow up		
		6 weeks	3 months	6 months
Demographics	X			
Anthropometrics	X	X	X	X
Clinical assessment	X	X	X	X
Arterial Blood Gas	X	X	X	X
Spirometry (full lung function)	(X)	X	X	(X)
Respiratory Sleep studies	X			X
Exercise capacity	X	X	X	X
HRQL	X	X	X	X
Compliance		X	X	X
Actigraphy (7 day)	X	X	X	X
Pulmonary Physiology (invasive)	(X)	X	(X)	(X)

7.1.6: Data analysis

Previous work from our group has shown a pre-post treatment improvement in HCVR of 1.4 l/min/kPa with a test standard deviation of 2.0 l/min/kPa.[137] Using an expected between group difference in HCVR of 2.0 l/min/kPa 40 patients are required (randomised on a 1:1 basis) to be 80% confident of detecting the difference at 6 weeks at the 0.05 level.

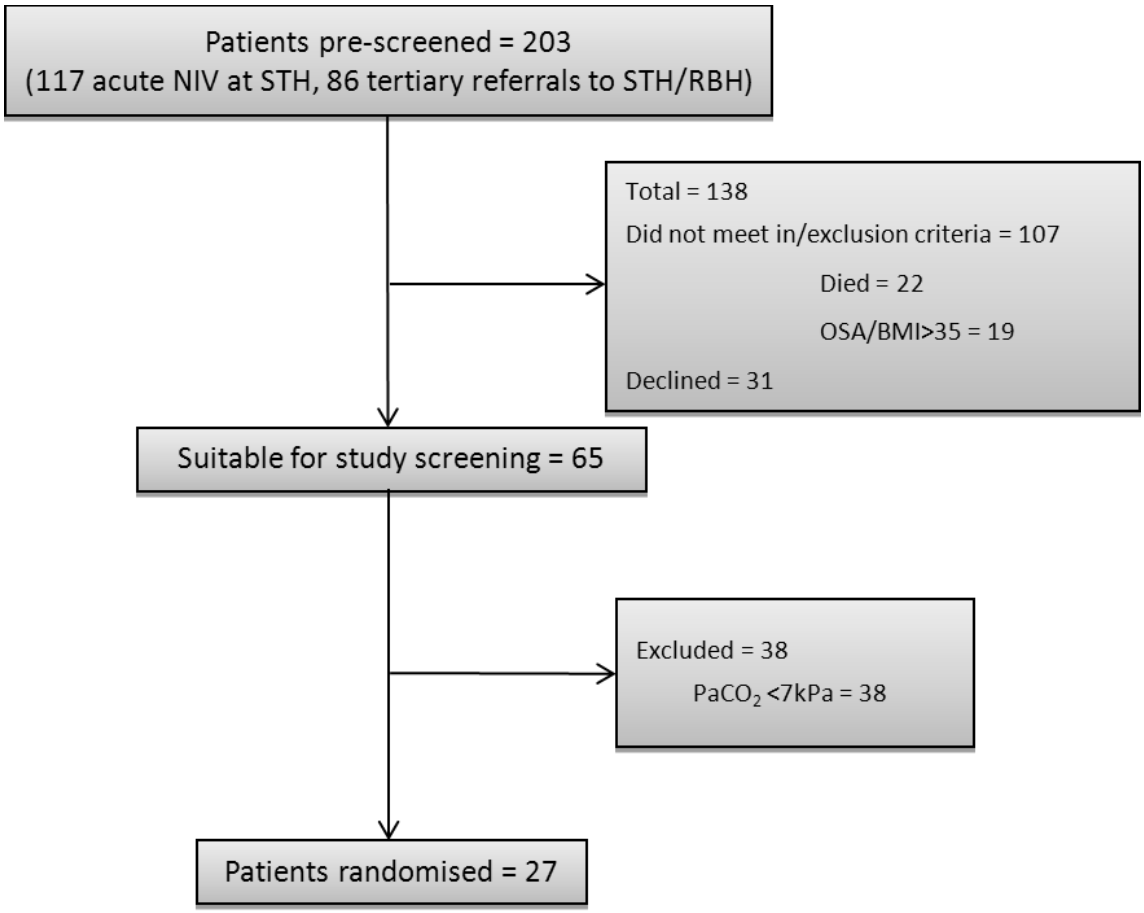
Data were analysed using independent or paired t-test where appropriate, unless demonstrably not normally distributed in which case an appropriate non-parametric equivalent was used. Parametric data are presented as mean ± standard deviation and non-parametric data as median (inter-quartile range). Correlation analyses were performed using Pearson's correlation test for parametric data and Spearman's rank test for non-parametric data. For all analyses, a p-value <0.05 was considered statistically significant. Data analyses were conducted using PASW statistics 18 (SPSS, Chicago, IL, USA).

7.2: Results

7.2.1: Patient recruitment

A consort flow diagram showing screening failures is provided in Figure 28.

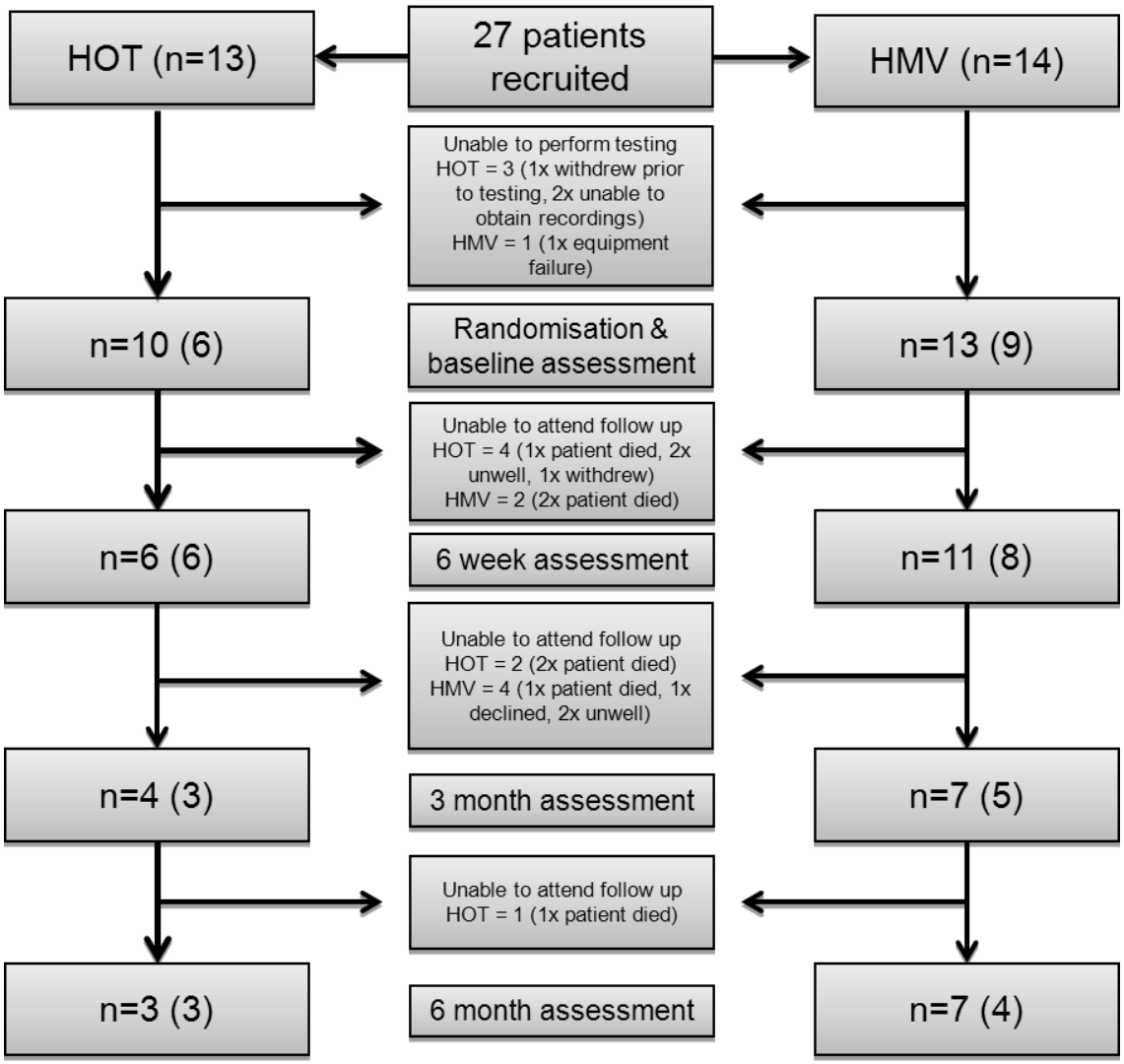
Figure 28: Consort diagram detailing screening for HOT-HMV UK trial at St Thomas' (STH) and the Royal Brompton (RBH) Hospitals for the physiological sub-study



Abbreviations: OSA – obstructive sleep apnoea, BMI – body mass index, $PaCO_2$ – arterial partial pressure of carbon dioxide.

A subset of 27 patients from the main study cohort were recruited with 23 patients (HOT=10, HMV=13) able to undergo baseline physiological testing. Details on recruitment and retention are provided in Figure 29.

Figure 29: Patient recruitment and retention for physiological assessment in HOT-HMV UK trial



Consort diagram detailing recruitment and follow up measurements with reasons for withdrawal or failure to complete testing. Numbers in brackets indicate those patients undergoing additional invasive measures of pulmonary mechanics with combined EMG and balloon oesophageal catheter. Abbreviations: HOT – home oxygen therapy, HMV – home mechanical ventilation, EMG – electromyogram.

7.2.2: Baseline data

Comparisons of baseline anthropometric, arterial blood gas analysis, and lung function testing data for the 23 patients who were randomised and completed physiological evaluation at baseline are provided in Table 26.

Table 26: Baseline data for patients undergoing physiological measurements in HOT-HMV UK trial: [A] Anthropometric and [B] Lung function

Table 26A: Anthropometric

	HOT	HMV	p-value
Centre (STH / RBH)	5 / 5	9 / 4	0.349
Age (years)	67 ± 10	67 ± 11	0.959
Gender (Male / Female)	3 / 7	8 / 5	0.133
Pack year history	55 ± 19	50 ± 17	0.520
BMI (kgm^{-2})*	24.6 ± 6.7	20.2 ± 2.9	0.044*
Weight (kg)	66.2 ± 21.3	54.0 ± 8.8	0.076
Fat free mass (kg)	33.2 ± 5.4	30.2 ± 7.7	0.306
Fat free mass index (kgm^{-2})	12.4 ± 1.5	11.3 ± 2.6	0.237
$PaCO_2$ (kPa)	7.9 ± 0.7	8.0 ± 0.8	0.743
PaO_2 (kPa)	6.5 ± 1.1	6.6 ± 1.1	0.922

*p<0.05. Abbreviations: HOT – home oxygen therapy, HMV – home mechanical ventilation, STH – St Thomas' Hospital, RBH – Royal Brompton Hospital, BMI – body mass index, $PaCO_2$ – arterial partial pressure of carbon dioxide, PaO_2 – arterial partial pressure of oxygen.

Table 26B: Lung function

	HOT	HMV	p-value
$PaCO_2$ (kPa)	7.9 ± 0.7	8.0 ± 0.8	0.743
PaO_2 (kPa)	6.5 ± 1.1	6.6 ± 1.1	0.922
Bicarbonate ($mmolL^{-1}$)	35 ± 3	38 ± 8	0.186
FEV_1 (L)	0.73 ± 0.34	0.54 ± 0.18	0.102
(%)	(30 ± 8)	(23 ± 11)	0.114
FVC (L)	1.86 ± 0.49	1.72 ± 0.82	0.640
(%)	(66 ± 11)	(52 ± 32)	(0.204)
FEV_1/FVC	0.38 ± 0.09	0.33 ± 0.08	0.232

	HOT	HMV	p-value
TLC (L)	5.35 ± 0.86	4.98 ± 0.87	0.434
(%)#	(105 ± 18)	(93 ± 26)	(0.326)
V_a (L)	3.57 ± 1.27	3.96 ± 0.74	0.559
(%)#	(65 ± 18)	(67 ± 12)	(0.852)
RV (L)	3.64 ± 0.67	3.04 ± 0.83	0.156
(%)#	(172 ± 30)	(142 ± 44)	(0.153)
FRC (L)	4.32 ± 0.82	3.81 ± 0.67	0.240
(%)#	(149 ± 35)	(130 ± 36)	(0.329)
DLCO (ml CO/min/kPa)	3.22 ± 2.15	1.71 ± 1.35	0.211
(%)#	(39 ± 22)	(26 ± 11)	(0.254)

#performed on HOT n=6, HMV n=8. Abbreviations: HOT – home oxygen therapy, HMV – home mechanical ventilation, $PaCO_2$ – arterial partial pressure of carbon dioxide, PaO_2 – arterial partial pressure of oxygen, FEV_1 – forced expiratory volume in 1s, FVC – forced vital capacity, TLC – total lung capacity, V_a – alveolar volume, RV – residual volume, FRC – functional residual capacity, DLCO – diffusion capacity of carbon monoxide.

The only statistically significant difference in baseline anthropometric and lung function characteristics was BMI (mean difference 4.4, 95%CI 0.1 to 8.7, p=0.044). There were no differences observed between groups at baseline in terms of respiratory muscle strength, resting breathing parameters, neural respiratory drive or hypercapnic response (Table 27) with the exception of parasternal muscle derived measures of neural respiratory drive which indicated higher levels of resting NRD in the group randomised to receive HMV (EMG_{para}%max mean difference -15%, 95%CI -1 to -28, p=0.035; $NRDI_{para}$ mean difference -355 AU, 95%CI -23 to -686, p=0.037). A non-significant trend towards a difference was present in EMG_{di}%max (mean difference -14%, 95%CI 2 to -29, p=0.086) again, with higher levels of resting drive in the patients randomised to HMV.

Table 27: Baseline measurement of: [A] Respiratory muscle strength, [B] Pulmonary mechanics and ventilation parameters and [C] Neural respiratory drive and hypercapnic response testing

Table 27A: Respiratory muscle strength

	HOT	**HMV**	p-value
SNIP (cmH_2O)	40 ± 13	36 ± 18	0.610
Sniff P_{oes} (cmH_2O)	53 ± 20	43 ± 16	0.292
Sniff P_{di} (cmH_2O)	66 ± 26	55 ± 19	0.341
MIP (cmH_2O)	28 ± 16	28 ± 15	0.946
MEP (cmH_2O)	46 ± 17	49 ± 22	0.755

Abbreviations: HOT – home oxygen therapy, HMV – home mechanical ventilation, SNIP – sniff nasal inspiratory pressure, P_{oes} – oesophageal pressure, MIP – mouth inspiratory pressure, MEP – mouth expiratory pressure.

Table 27B: Pulmonary mechanics and ventilation parameters

	HOT	**HMV**	p-value
IC (mL)	1342 ± 442	1339 ± 546	0.990
MVV ($Lmin^{-1}$)	19.8 ± 6.1	17.1 ± 4.4	0.247
$_{dyn}PEEP_i$ (cmH_2O)	3.9 ± 2.3	3.9 ± 4.4	0.992
C_{dyn} (ml/cmH_2O)	181 ± 103	134 ± 75	0.325
V_t (ml)*	515 ± 114	587 ± 172	0.268
RR (breaths per minute)	23 ± 6	21 ± 7	0.536
V_e	11.6 ± 3.2	11.6 ± 3.3	0.993

Abbreviations: HOT – home oxygen therapy, HMV – home mechanical ventilation, IC – inspiratory capacity, MVV – maximum voluntary ventilation, $_{dyn}PEEP_i$ – dynamic intrinsic positive end-expiratory pressure, C_{dyn} – dynamic compliance, V_t – tidal volume, RR – respiratory rate, V_e – minute ventilation.

Table 27C: Neural respiratory drive and hypercapnic response testing

	HOT	HMV	p-value
$EMG_{para\%max}$ (%)*	17 ± 9	32 ± 19	0.035*
$EMG_{di\%max}$ (%)	30 ± 16	44 ± 13	0.086
$NRDI_{para}$ (AU)*	359 ± 135	714 ± 487	0.037*
$NRDI_{di}$ (AU)	804 ± 497	925 ± 365	0.596
HCVR ($Lmin^{-1}$/kPa)	2.76 ± 3.14	1.46 ± 1.14	0.213
$HCEMG_{para\%max}R$ (%/kPa)	8.58 ± 5.23	6.94 ± 5.66	0.499
$HCEMG_{di\%max}R$ (%/kPa)	10.66 ± 11.98	8.81 ± 6.29	0.712

*p<0.05. Abbreviations: HOT – home oxygen therapy, HMV – home mechanical ventilation, $EMG_{para\%max}$ – percentage of maximum obtainable parasternal electromyogram, $EMG_{di\%max}$ – percentage of maximum obtainable diaphragm electromyogram, $NRDI_{para}$ – neural respiratory drive index of the parasternal muscle, $NRDI_{di}$ – neural respiratory drive index of the diaphragm, HCVR – hypercapnic ventilatory response, $HCEMG_{para\%max}R$ – hypercapnic parasternal muscle electromyogram response, $HCEMG_{di\%max}R$ – hypercapnic diaphragm electromyogram response.

7.2.3: Assessment of severity of sleep disordered breathing

There were no significant differences demonstrated between patients subsequently randomised to HOT or HMV on either diagnostic limited overnight respiratory polygraphy or oximetry-capnometry performed on prescribed oxygen level (Table 28).

Table 28: Comparison of pre-randomisation limited overnight respiratory polygraphy: [A] Diagnostic testing and [B] Oxygen safety testing

Table 28A: Diagnostic testing

	HOT	HMV	p-value
Diagnostic study performed on (oxygen / room air)	7 / 2	11 / 2	0.683
AHI (events/hour)	5 ± 8	10 ± 20	0.473
4%ODI (events/hour)	19 ± 21	17 ± 34	0.861
Mean SpO_2 (%)	89 ± 9	93 ± 5	0.181
Min SpO_2 (%)	64 ± 22	68 ± 16	0.609
%TST SpO_2<90% (%)	35 ± 39	22 ± 26	0.352
Mean $tcCO_2$ (kPa)	9.0 ± 0.9	9.0 ± 1.5	0.925
Max $tcCO_2$ (kPa)	10.1 ± 1.1	10.4 ± 1.8	0.587

Abbreviations: HOT – home oxygen therapy, HMV – home mechanical ventilation, AHI – apnoea-hypopnoea index, ODI – oxygen desaturation index, SpO_2 – oxyhaemaglobin saturation, TST – total sleep time, $tcCO_2$ – transcutaneous carbon dioxide.

Table 28B: Oxygen safety testing

	HOT	HMV	p-value
Oxygen prescription ($Lmin^{-1}$)	1.3 ± 0.8	1.1 ± 0.6	0.514
4%ODI (events/hour)	17 ± 20	10 ± 16	0.369
Mean SpO_2 (%)	90 ± 9	93 ± 5	0.204
Min SpO_2 (%)	66 ± 21	68 ± 17	0.761
%TST SpO_2<90% (%)	31 ± 38	20 ± 26	0.447
Mean $tcCO_2$ (kPa)	9.1 ± 0.9	9.3 ± 1.4	0.622
Max $tcCO_2$ (kPa)	10.1 ± 1.1	10.8 ± 1.7	0.331

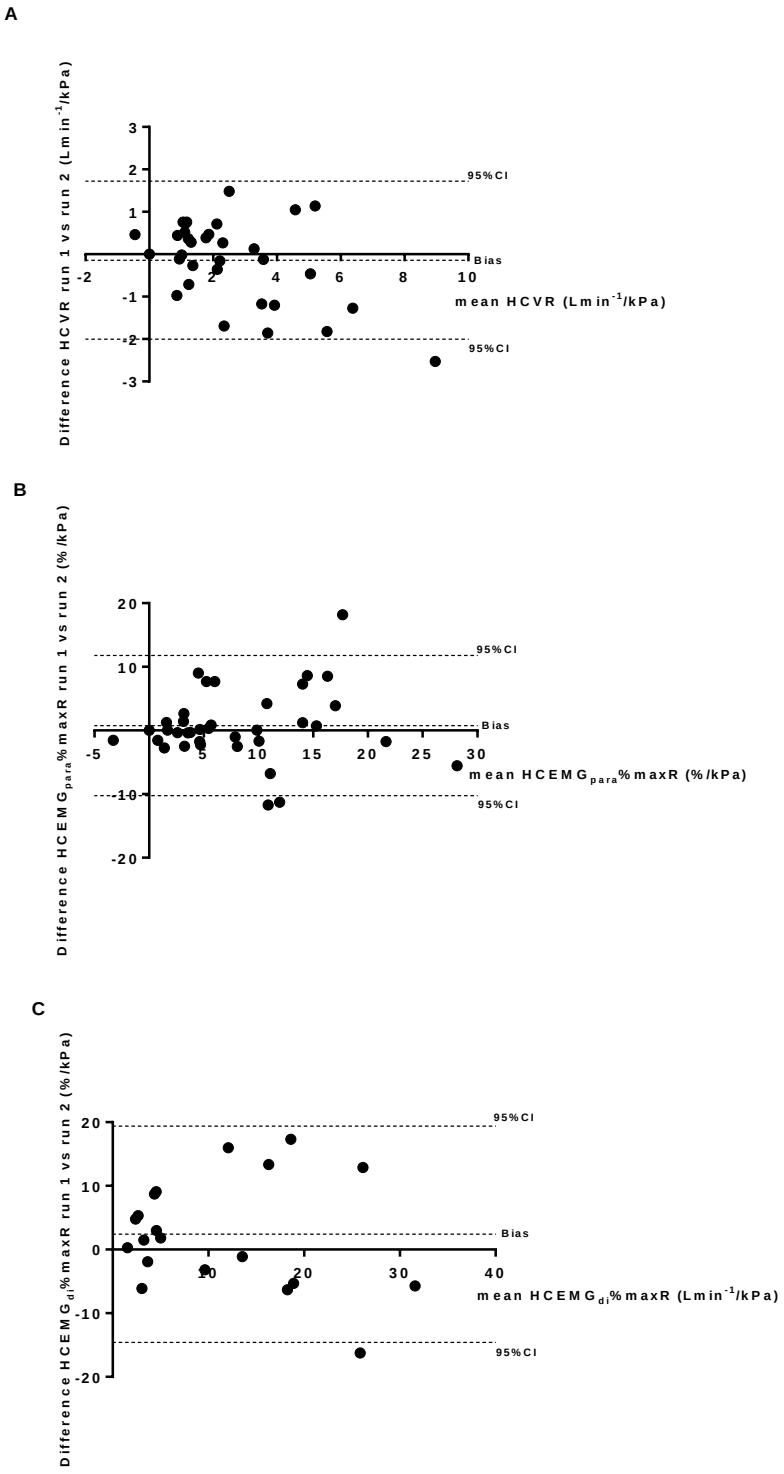
Abbreviations: HOT – home oxygen therapy, HMV – home mechanical ventilation, AHI – apnoea-hypopnoea index, ODI – oxygen desaturation index, SpO_2 – oxyhaemaglobin saturation, TST – total sleep time, $tcCO_2$ – transcutaneous carbon dioxide.

There were no significant correlations demonstrated between nocturnal hypoxia (mean nocturnal SpO_2 and %night time SpO_2<90%), nocturnal hypercapnia (mean $tcCO_2$ and max $tcCO_2$) on prescribed oxygen therapy and measurements of hypercapnic responsiveness (HCVR, $HCEMG_{para}R$ and $HCEMG_{di}R$), pulmonary mechanics and resting neural respiratory drive. Daytime resting V_e demonstrated an inverse correlation with mean nocturnal $tcCO_2$ (r=-0.556, p=0.006) and max nocturnal $tcCO_2$ (r=-0.424, p=0.044). As expected mean nocturnal $tcCO_2$ correlated with daytime $PaCO_2$ whether performed on room air (r=0.449, p=0.028) or on prescribed oxygen therapy (r=0.422, p=0.040). Nocturnal mean SpO_2 correlated with daytime SpO_2 on prescribed oxygen (r=0.536, p=0.007) but there was no correlation between nocturnal mean SpO_2 and daytime SpO_2 on room air (r=0.018, p=0.934).

7.2.4: Repeatability of hypercapnic responsiveness testing

The slopes of sequential HCVR tests performed during a single session showed good repeatability with a bias of -0.1 $Lmin^{-1}$/kPa, 95%CI 1.7 to -2.0 and acceptable levels of repeatability for $EMG_{para\%max}$ ($HCEMG_{para\%max}R$) with a bias of 0.8 %/kPa, 95%CI -10.3 to 11.8 and $EMG_{di\%max}$ ($HCEMG_{di\%max}R$) with a bias of 2.4 %/kPa, 95%CI -14.6 to 19.4 (Figure 30).

Figure 30: Bland-Altman plots demonstrating reproducibility of hypercapnic responsiveness testing for [A] ventilation (HCVR), [B] percentage of maximum obtainable parasternal muscle electromyogram ($HCEMG_{para\%max}R$) and [C] percentage of maximum obtainable diaphragm electromyogram ($HCEMG_{di\%max}R$)



7.2.5: Efficacy of HMV to control sleep disordered breathing and ventilatory settings

9 patients were discharged with a Harmony 2 machine (Philips-Respironics, PA, US) and 4 patients with a VPAP III STa machine (ResMed, Bella Vista, Australia). Discharge non-invasive ventilator settings for the HMV group were IPAP 26 ± 2 cmH_2O, EPAP 4 ± 1 cmH_2O and back up rate 15 ± 2 bpm. All patients were discharged with a full face mask. Oximetry-capnometry performed on discharge ventilator settings showed a significant reduction in $tcCO_2$ and improvement in nocturnal saturations between diagnostic and therapeutic overnight limited respiratory polygraphy in the HMV group (Table 29). There were also significant between group differences in the severity of nocturnal hypoxia and hypercapnia between HOT and HMV groups (Table 29).

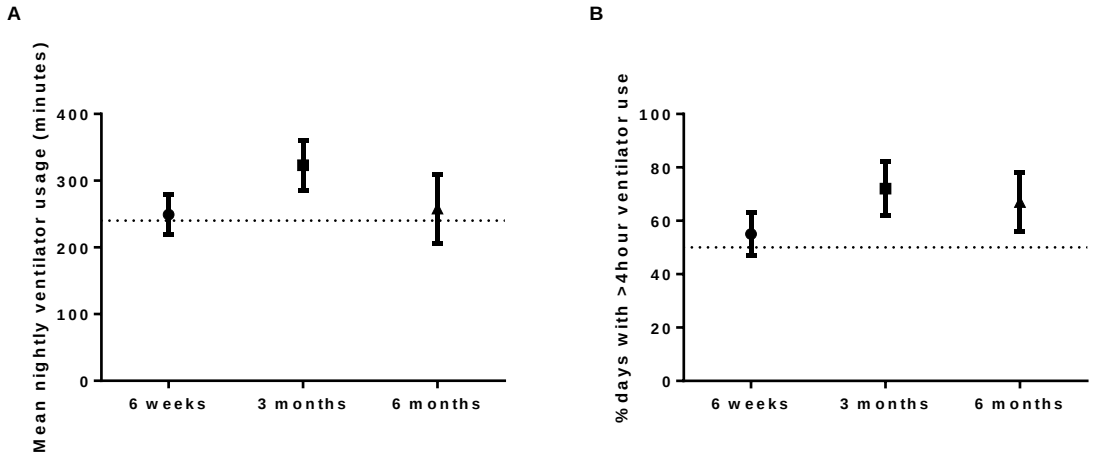
Table 29: Comparison of oximetry-capnometry on home oxygen therapy (HOT) and home mechanical ventilation (HMV)

	HOT	**HMV**	p-value
4%ODI	10 ± 16	9 ± 9	0.866
Mean SpO_2 (%)	92 ± 6	96 ± 3$^{\#}$	0.060
Min SpO_2 (%)	74 ± 14	81 ± 11$^{\#}$	0.186
%TST SpO_2<90% (%)	18 ± 30	7 ± 13$^{\#}$	0.235
Mean $tcCO_2$ (kPa)*	9.0 ± 0.9	7.6 ± 1.4$^{\#}$	0.011*
Max $tcCO_2$ (kPa)*	10.0 ± 1.1	8.9 ± 1.5$^{\#}$	0.049*

$^{*}p<0.05$ between group comparison (independent t-test); $^{\#}p<0.05$ within group improvement from diagnostic sleep study (paired t-test). Abbreviations: HOT – home oxygen therapy, HMV – home mechanical ventilation, ODI – oxygen desaturation index, SpO_2 – oxyhaemaglobin saturation, TST – total sleep time, $tcCO_2$ – transcutaneous carbon dioxide.

Adequate levels of adherence with nocturnal ventilation were demonstrated throughout follow up in patients randomised to HMV (Figure 31).

Figure 31: Adherance with home mechanical ventilation (HMV) throughout follow up represented by [A] mean nightly ventilator usage and [B] percentage of nights with >4 hours of ventilator use



7.2.6: Changes in neural respiratory drive

There were significant improvements in neural respiratory drive as demonstrated by increase in both HCVR and $HCEMG_{para\%max}R$ between baseline and 6 week follow up that persisted at 3 month follow up for $HCEMG_{para\%max}R$ although the treatment effect was attenuated in the HCVR (Table 30). There were no within or between group changes in $HCEMG_{di\%max}R$ at 3 month follow up.

Table 30: Change from baseline to follow up at 6 weeks and 3 months in hypercapnic response testing in patients randomised to home oxygen therapy (HOT) or home mechanical ventilation (HMV)

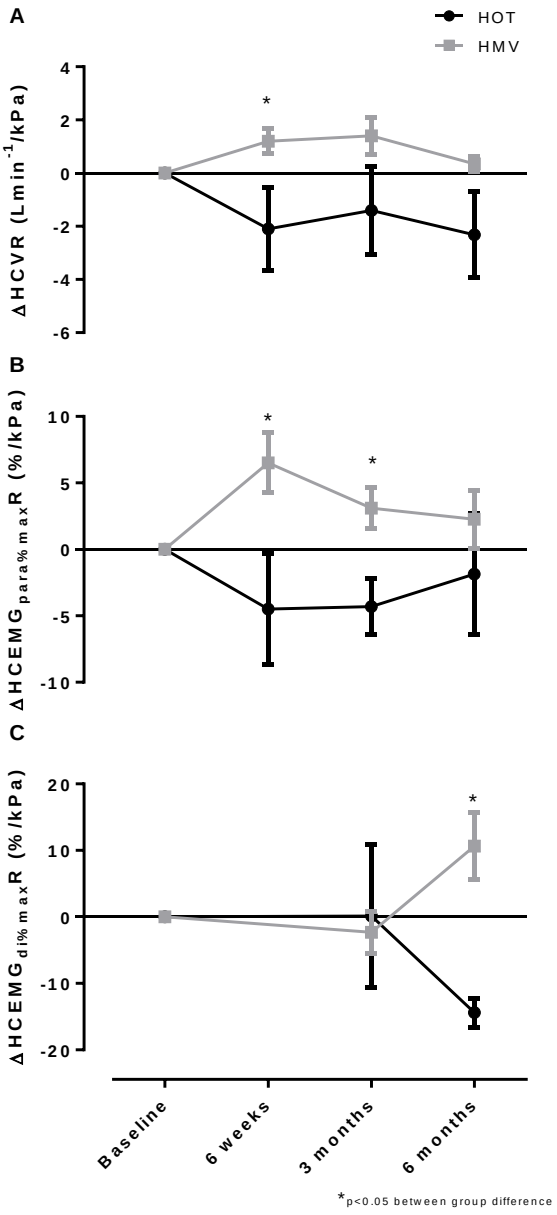
	Δ Baseline to 6 week follow up				**Δ Baseline to 3 month follow up**			
	HOT	**HMV**	Mean difference (95%CI)	p-value	**HOT**	**HMV**	Mean difference (95%CI)	p-value
ΔHCVR ($Lmin^{-1}$/kPa)	-2.1 ± 3.8	1.2 ± 1.3*	3.3 (0.1 to 6.4)	0.043	-1.4 ± 3.7	1.4 ± 1.7	2.8 (-1.0 to 6.6)	0.134
Δ$HCEMG_{para\%max}R$ (%/kPa)	-4.5 ± 10.3	6.5 ± 6.4*	10.9 (1.2 to 20.7)	0.031	-4.3 ± 4.7*	3.1 ± 3.8	7.4 (1.6 to 13.2)	0.018
Δ$HCEMG_{di\%max}R$ (%/kPa)					0.1 ± 18.6	-2.3 ± 7.0	-2.4 (-24.2 to 19.4)	0.795

*p<0.05 within group paired change from baseline. Abbreviations: HOT – home oxygen therapy, HMV – home mechanical ventilation, HCVR – hypercapnic ventilatory response,

$HCEMG_{para\%max}R$ – hypercapnic parasternal muscle electromyogram response, $HCEMG_{di\%max}R$ – hypercapnic diaphragm electromyogram response.

Treatment effect on hypercapnic response testing was further attenuated at 6 months (Figure 32).

Figure 32: Changes in hypercapnic response testing between baseline and follow up for [A] hypercapnic ventilatory response (HCVR), [B] hypercapnic parasternal muscle electromyogram response ($HCEMG_{para\%max}R$) and [C] hypercapnic diaphragm electromyogram response ($HCEMG_{di\%max}R$)

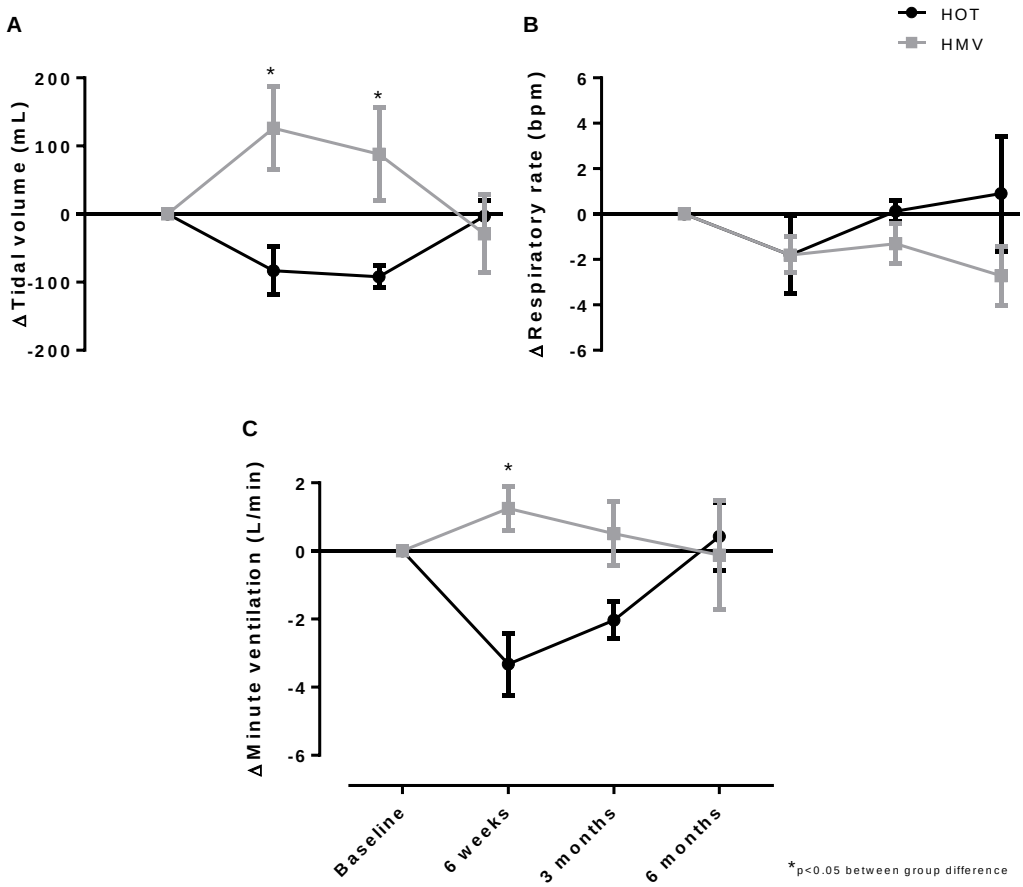


Abbreviations: HOT – home oxygen therapy, HMV – home mechanical ventilation, HCVR – hypercapnic ventilatory response, $HCEMG_{para}R$ – hypercapnic parasternal muscle electromyogram response, $HCEMG_{di}R$ – hypercapnic diaphragm electromyogram response.

7.2.7: Changes in tidal breathing, respiratory cycle, pulmonary mechanics and gas exchange between baseline, 6 weeks follow up and 3 months follow up

Patients randomised to HOT had a significant reduction in resting V_e at both 6 weeks (Δ-3.3 $Lmin^{-1}$, 95%CI 1.0 to 5.7, p=0.015) and 3 months follow up (Δ-2.0 $Lmin^{-1}$, 95%CI 0.6 to 3.4, p=0.014) that resulted in a significant between group difference in change in V_e from baseline to 6 weeks between HOT and HMV groups (Δ4.6 $Lmin^{-1}$, 95%CI 2.2 to 6.9, p=0.001) and a trend towards a difference at 3 months (Δ2.5 $Lmin^{-1}$, 95%CI -0.1 to 5.1, p=0.056). There was a trend towards improved V_t (Δ126 mL, 95%CI -11 to 264, p=0.068) and RR (Δ-1.8 bpm, 95%CI -3.4 to 0.8, p=0.055) in the HMV group at 6 weeks (Figure 33). The HOT group had a reduction in V_t at 6 weeks (Δ-83 mL, 95%CI -173 to 6, p=0.063) that further reduced at 3 months (Δ-92 mL, 95%CI -160 to -51, p=0.002). These reductions in V_t in the HOT group coupled with the trends to improved V_t in the HMV group led to significant between group differences at 6 weeks (Δ210 mL, 95%CI 29 to 390, p=0.026) and 3 months (Δ180 mL, 95%CI 3 to 358, p=0.047).

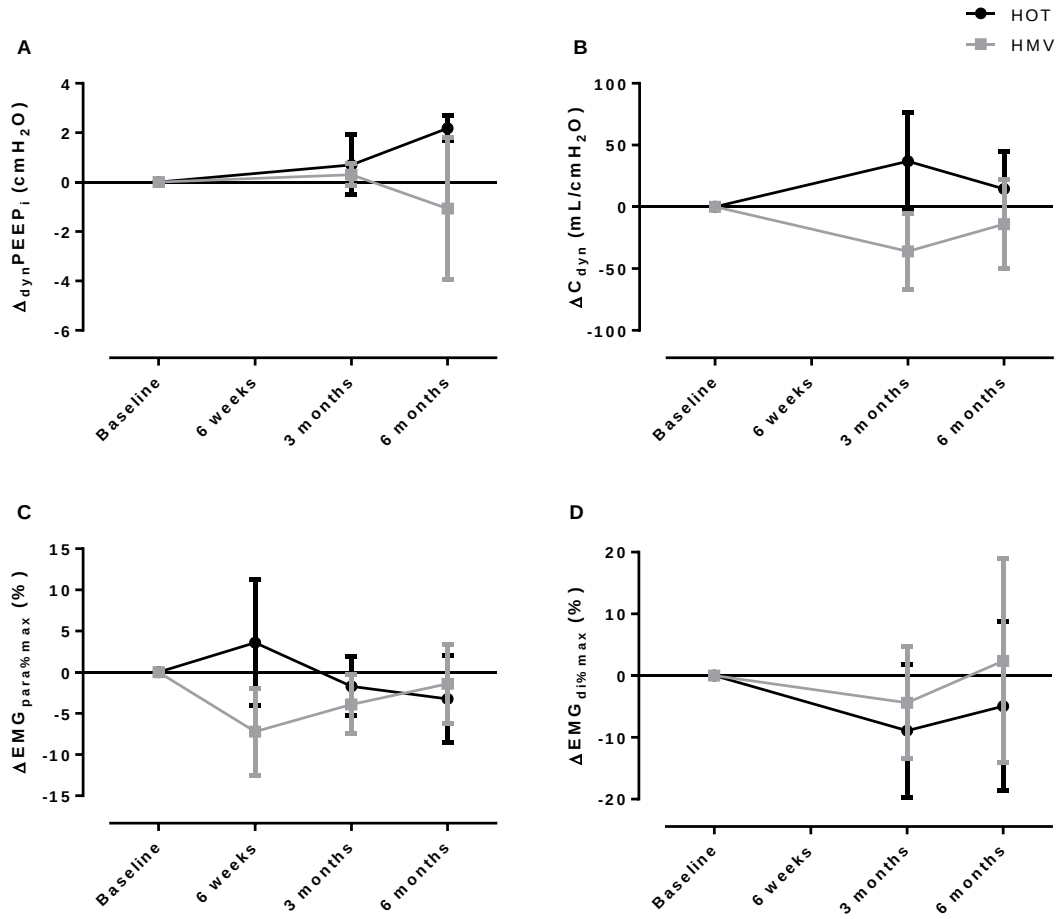
Figure 33: Comparison between home oxygen therapy (HOT) and home mechanical ventilation (HMV) groups of changes from baseline at 6 week, 3 month and 6 month follow up for [A] tidal volume, [B] respiratory rate and [C] minute ventilation



Abbreviations: HOT – home oxygen therapy, HMV – home mechanical ventilation.

There were no within or between group differences in changes in respiratory cycle, including inspiratory time (T_i), expiratory time (T_e) or duty cycle (T_i/T_{tot}), between baseline and follow up at 6 weeks and 3 months. Furthermore, there were no demonstrable changes in either C_{dyn} or $_{dyn}PEEP_i$, resting $EMG_{para\%max}$ and resting $EMG_{di\%max}$ at 3 months follow up (Figure 34).

Figure 34: Changes in resting respiratory mechanics and neural respiratory drive between baseline and follow up in home oxygen therapy (HOT) and home mechanical ventilation (HMV) groups for [A] dynamic intrinsic positive end-expiratory pressure (dynPEEPi), [B] dy



Abbreviations: HOT – home oxygen therapy, HMV – home mechanical ventilation, IC – inspiratory capacity, MVV – maximum voluntary ventilation, $_{dyn}PEEP_i$ – dynamic intrinsic positive end-expiratory pressure, C_{dyn} – dynamic compliance, $EMG_{para\%max}$ – percentage of maximum obtainable parasternal electromyogram, $EMG_{di\%max}$ – percentage of maximum obtainable diaphragm electromyogram.

Significant within group improvement in $PaCO_2$ occurred in the HMV group at 6 weeks (Δ-0.9 kPa, 95%CI -0.5 to -1.4, p=0.001) and at 3 months (Δ-0.9 kPa, 95%CI -0.4 to -1.5, p=0.004). There was no significant change in $PaCO_2$ in the HOT group at 6 week (Δ-0.3 kPa, 95%CI -1.7 to 1.1, p=0.621) and 3 months (Δ-0.7 kPa, 95%CI -1.5 to 0.2, p=0.101). A trend towards improved PaO_2 was shown in the HMV group at 6 weeks (Δ0.6 kPa, 95%CI 0.0 to 1.1, p=0.059) that became a significant improvement by 3 months (Δ1.0 kPa, 95%CI 0.2 to 1.7,

p=0.016). There were no significant improvements observed in PaO_2 in the HOT group at 6 weeks (Δ0.2 kPa, 95%CI -0.9 to 1.3, p=0.720) and 3 months follow up (Δ0.5 kPa, 95%CI -0.8 to 1.8, p=0.372). Despite the within group changes there were no significant between group differences demonstrated during follow up.

7.3: Discussion

These data represent the first randomised controlled physiological study to investigate long term effects of home mechanical ventilation and home oxygen therapy compared to home oxygen therapy alone. The data have demonstrated the addition of nocturnal domiciliary NIV to oxygen therapy improves central respiratory drive and leads to augmented diurnal tidal volume.

7.3.1: Critique of the method

Patient recruitment

The study failed to recruit the pre-specified number of patients leading it to be underpowered to detect a difference between the groups in terms of change in hypercapnic ventilatory response. The trial started on schedule, but patient recruitment to the trial was slow although it must be highlighted that these are an extremely sick group of patients that often declined recruitment to the physiological sub-study, even if they agreed to be enrolled in the clinical trial. This slow accrual persisted despite numerous attempts to increase local referrals as well as maximising in-house recruitment. The reasons that contributed to the low recruitment rate are detailed below:

1. There were more patients than expected, from our own previous pilot data, that had clinically improved by the 2 week screening period and subsequently had a $PaCO_2$ less than 7.0 kPa.
2. There was a higher than expected proportion of patients with obesity and obstructive sleep apnoea, reflecting general population trends.
3. There was a larger than expected refusal by the patients to take part in the trial and as highlighted above there was further refusal to be part of the physiological sub-study. This refusal to be part of the trial was driven by the patients' negative experience of non-invasive ventilation during

the acute illness, which contributed to their reluctance to trial the therapy at home.

4. A large proportion of patients died prior to screening both during the acute episode and following discharge.
5. Recruitment rate was affected by a fall in COPD patients receiving non-invasive ventilation for management of acute hypercapnic respiratory failure period. Specifically, at St Thomas, there were 58 COPD patients in 2010 and only 44 patients in 2011 that were managed with acute use of non-invasive ventilation.

Patient retention

There was a significant loss of follow up data due to patient death or severe inter-current illness preventing assessment. The magnitude of lost patient follow up data is perhaps not surprising given the acknowledged high morbidity and mortality in this patient population.[146, 147, 149] Combined with the poor recruitment, the poor patient retention contributed to the under powering of the study. Previous studies have used stable patients to investigate the physiological mechanisms of HMV in this patient population in order to overcome this problem.[135, 235] Despite this approach, there has been no clear clinical efficacy demonstrated in this infrequent exacerbator phenotype[93, 138, 140] and as such a patient population considered to have the greatest potential for clinical benefit was selected for this trial. Notwithstanding these factors, the primary outcome of the study was a change in hypercapnic ventilator response, which was shown to have a significant within group difference from baseline in the HMV group that translated to a treatment effect when compared to the control group at 6 weeks. The magnitude of this change was similar to that observed in earlier uncontrolled studies,[137] although the small patient numbers resulted in a less accurate prediction of the true treatment effect than would have been achieved had the study reached full recruitment.

Control of nocturnal hypoventilation

A critique of much of the published data, that fails to show a clear clinical or physiological advantage of using domiciliary NIV in hypercapnic COPD, is the failure of the studies to demonstrate a clear therapeutic effect on nocturnal hypoventilation.[133] Studies that have shown a therapeutic effect have included

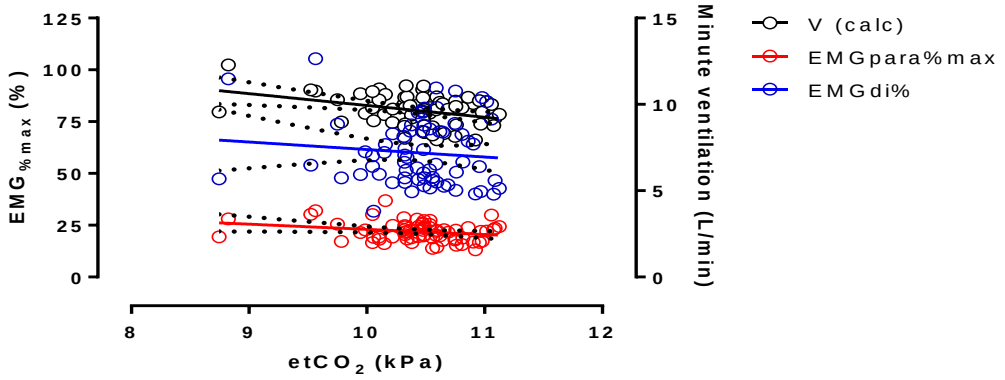
those in which a high pressure strategy was adopted and nocturnal hypoventilation improved.[136] We have demonstrated a clear within and between group treatment effect of NIV on the control of nocturnal $tcCO_2$ with high pressure NIV. Interestingly, in contrast to published data in less severe patients there was no relationship demonstrated between hypercapnic ventilatory response and nocturnal hypoxia, measured as either mean oxygen saturation or percentage of total sleep time less than 90%.[241] This is perhaps to be expected given that all patients in the current study had a reduced hypercapnic ventilatory response with more severe airflow limitation and worse gas exchange than patients in the earlier study by Vos *et al*. The relationship between daytime ventilation and nocturnal hypoventilation can be inferred to show that the cause of the profound nocturnal hypoventilation is the result of the normal changes that occur during sleep being imposed on an respiratory system with severely abnormal pulmonary mechanics.

Techniques to measure neural respiratory drive and hypercapnic ventilatory response

The measurement of NRD using EMG_{di} has been previously shown to be reproducible and reflect disease severity in COPD.[53] The use of EMG_{para} to represent NRD in stable COPD has been described in detail earlier in this work and it has been shown to have acceptable levels of reproducibility in this patient population. The measurement of the HCVR via the rebreathe technique has been shown to be reliable and reproducible even in the presence of airway obstruction, as occurs in COPD.[237] Inconsistent approaches have been adopted in an attempt to 'normalise' the HCVR in COPD to reflect the mechanical constraints on the respiratory system that limit changes to minute ventilation. Such approaches have included dividing the slope of the HCVR by FEV_1, measured MVV and predicted MVV.[137, 299] In the current study, it was not felt that adjusting the raw HCVR was warranted. This was because the use of EMG_{para} and EMG_{di} would reflect central respiratory drive, negating the need to control for airflow obstruction and respiratory mechanical limitation. In addition, the use of a randomised controlled design allows for direct comparison between the two groups without the need to normalise the data for comparison to a healthy population. The values for HCVR in the study population were lower

than those reported in earlier work for eucapnic and hypercapnic COPD.[137, 237] The strength of the relationship between end-tidal carbon dioxide and minute ventilation was also weaker than earlier reports with some patients not showing a linear response to the hypercapnic challenge. This could be explained in a number of ways principally that either the test was inadequate to demonstrate the hypercapnic ventilatory response or the patient no longer has a genuine linear response to progressive hypercapnia. The former relates to the established phenomenon of a 'dog leg' between minute ventilation and level of carbon dioxide observed in the HCVR test. This occurs because arterial carbon dioxide needs first to rise to a threshold level in order to stimulate central respiratory centres.[234] It is possible that these patients with non-linear responses had yet to reach the 'threshold' level of hypercapnia. However, patients were subjected to a significant degree of hypercapnia until completion of the rebreathe period, or more commonly, patient intolerance. All traces were visually inspected to ensure a significant and linear rise in end-tidal carbon dioxide over time to be classed as technically adequate. There would be significant clinical safety concerns from attempting to produce more pronounced hypercapnia or to continue testing beyond patient tolerance in this group with severe COPD and recent exacerbation. Furthermore, several patients demonstrated a linear negative response to hypercapnic challenge, in that they had a decrease in both minute ventilation and markers of neural respiratory drive ($EMG_{para\%max}$ and $EMG_{di\%max}$) with progressive rise in end tidal carbon dioxide. An example hypercapnic challenge test of such a patient is provided for illustration (Figure 35).

Figure 35: Individual patient hypercapnic responsiveness testing demonstrating a negative relationship between end-tidal carbon dioxide (etCO2) and both minute ventilation (Ve) and neural respiratory drive (NRD)



Abbreviations: $EMG_{para\%max}$ – percentage of maximum obtainable parasternal electromyogram, $EMG_{di\%max}$ – percentage of maximum obtainable diaphragm electromyogram, $etCO_2$ – end-tidal carbon dioxide.

It can be presumed therefore that these patients have a hypercapnic 'threshold' that is sufficiently high as to be ineffective in response to an insult such as an acute exacerbation of COPD.

7.3.2: Changes in central respiratory drive

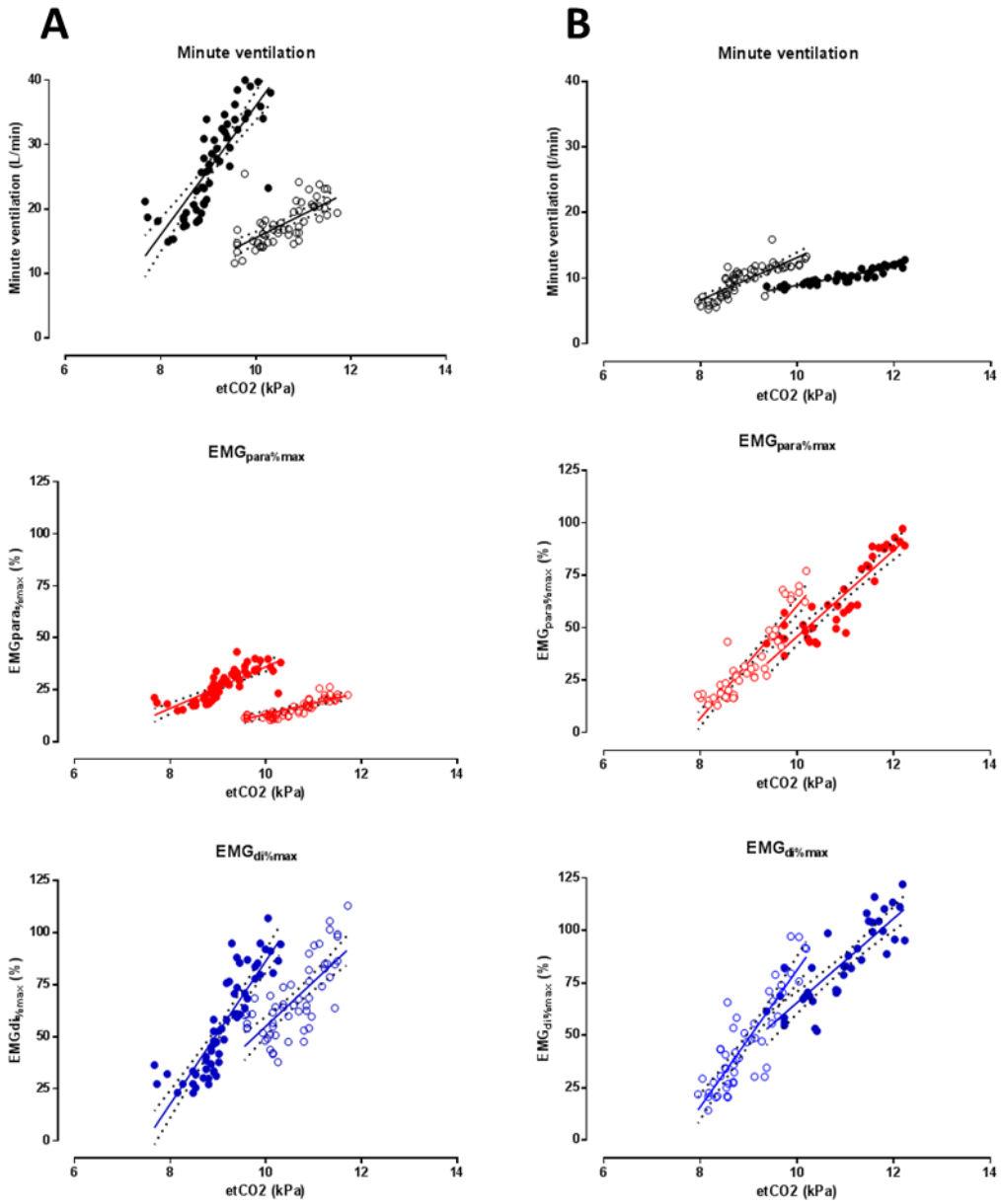
The use of domiciliary NIV to control nocturnal hypoventilation led to an improvement in both mechanical (hypercapnic ventilatory response) and neural (hypercapnic parasternal electromyogram response) response to carbon dioxide at the 6 week follow up stage. The improvement in neural respiratory drive was greater than that of mechanical respiratory drive and persisted for longer during follow up. This is to be expected given the particularly severe phenotype of COPD recruited for this study, specifically, patients with persistent severe hypercapnic respiratory failure as a consequence of severe airways obstruction following a recent hospital admission requiring acute non-invasive ventilation. The magnitude of improvement in the HMV group was similar to that seen in previous studies.[137]

Of interest, a non-significant reduction in both neural and mechanical respiratory drive was observed in the control group. Reductions in hypercapnic ventilatory response have been demonstrated in COPD patients following

administration of oxygen therapy.[300] However, the majority of our patients were already established on LTOT and thus this is less likely to have been a significant factor. The study design randomised patients in the weeks that followed an acute decompensated exacerbation necessitating treatment with NIV. As has been shown previously, re-setting of central respiratory drive occurs rapidly, within 5 days, with the administration of nocturnal NIV in the setting of chronic respiratory failure and a similar effect can be expected in the acute setting.[137] The attenuation of this improvement may be responsible for the loss of hypercapnic responsiveness in the control group during follow up contributing to the significant between group differences seen in this study.

Both the intervention and control groups experienced a reduction in $PaCO_2$ during follow up, although this was only significant in the HMV group suggesting that changes in hypercapnic response were not purely due to altered resting $PaCO_2$ levels. To provide further clarity, individual traces are provided for patient in the control and treatment groups demonstrating the changes in hypercapnic challenge testing (Figure 36). The traces illustrate the decrease both in slope and volume of response, indicating that patients in the control group have not only a reduced response to rising end-tidal carbon dioxide but also have a lower level of either ventilation or NRD at a given end-tidal carbon dioxide. In contrast, the opposite changes occur in the HMV group with both a higher level of both ventilation and NRD for a given end-tidal carbon dioxide with an enhanced response to rising hypercapnia.

Figure 36: Individual response to hypercapnic challenge in an example patient from [A] home oxygen therapy (HOT) and [B] home mechanical ventilation (HMV) groups



Closed circles represent data from single hypercapnic challenge test at baseline. Open circles represent repeat testing at 3 month follow up. Abbreviations: $EMG_{para\%max}$ – percentage of maximum obtainable parasternal electromyogram, $EMG_{di\%max}$ – percentage of maximum obtainable diaphragm electromyogram, $etCO_2$ – end-tidal carbon dioxide.

7.3.3: Changes in tidal breathing mechanics

There are conflicting current data on the changes in respiratory mechanics following domiciliary NIV in COPD. Studies have shown reduction in gas trapping,[134, 137] improved FEV_1,[135, 236] and reduced dynamic intrinsic PEEP.[236] The current study did not demonstrate a clear difference between groups in any

of these parameters. Changes in gas trapping were designed to be evaluated at 6 month follow up in the current study protocol but insufficient patient numbers reached this stage to allow meaningful use of inferential statistics, although the raw data shows trends in line with the published data. The changes in spirometry have been present only in the studies from Diaz *et al*[135, 236] and are not replicated in work by other groups.[137, 235] Changes in spirometry were also not seen in the recently published work by Funk *et al*[151] which utilised a similar patient population but adopted a different study design to our current study. Funk and colleagues recruited patients established on NIV following an acute exacerbation requiring mechanical ventilation 6 months following stabilisation and randomised them to either withdrawal or continuation of NIV. The use of this frequent exacerbator phenotype and the longer duration of our study than that of the previous work by Diaz *et al* or Nava *et al* leads to the confounding influence of inter-current exacerbations on lung function and other physiological parameters. Recent data has suggested that even a single exacerbations can cause deterioration in lung function and therefore potentially influence the findings of such studies.[301] In addition, changes in dynamic intrinsic PEEP have only been demonstrated in a single sham study that utilised diurnal rather than nocturnal NIV and thus may represent a specific effect of the therapy utilised in this modality. Also analysis of the data from this study demonstrates a large number of data points clustered with little change in either $PaCO_2$ or dynamic intrinsic PEEP and a small number of outlying data points driving the treatment effect.

A clear treatment effect was demonstrated in the HMV group by improved minute ventilation during follow up. The magnitude at 6 weeks in the current study (Δ1.2 L/min, 95%CI -0.2 to 2.7, p=0.091) was similar to that seen in the Diaz study at 4 weeks (Δ1.2 L/min, 95%CI 0.1 to 2.3, p<0.05). Changes in tidal volume in the current study at 6 weeks (Δ126 mL) were also consistent with the data published by Nava *et al* (Δ148 mL)[235] and Diaz *et al* (Δ181 mL)[236]. These changes in tidal breathing were not mirrored by changes in the respiratory cycle or in changes in measured load during the current study. As explained above, the study design using frequent exacerbators and the high loss of follow up data during the study may be responsible, in part, for this effect. In particular, it is

noteworthy that the effects demonstrated in the earlier studies were at a shorter follow up interval with the current study assessment of load was designed to be evaluated later at 3 months (C_{dyn}, $_{dyn}PEEP_i$ and spirometry) and 6 months (C_{dyn}, $_{dyn}PEEP_i$ and spirometry, gas trapping) when these treatment effects had been attenuated.

Surprisingly, the study did not demonstrate changes in resting NRD as reflected by either $EMG_{para\%max}$ or $EMG_{di\%max}$. This is in contrast to the clear changes in central respiratory drive during the hypercapnic challenge tests. Again, the assessment of $EMG_{di\%max}$ at 3 months follow up when other measures had started to attenuate may, in part, explain this finding. However, $EMG_{para\%max}$ was assessed at the 6 week stage when the other parameters of both tidal breathing and hypercapnic responsiveness showed demonstrable change. Whilst $EMG_{para\%max}$ reflects changes in respiratory load during acute exacerbations in COPD, via changes in lung volume and in particular inspiratory capacity, which in the current study did not significantly alter during follow up and explains the failure to demonstrate change at this time.[302] Although not significantly different due to the large spread of data, the group means moved in opposite directions with a reduction in $EMG_{para\%max}$ in the HMV group and an increase in the HOT group. Again, the small number of data points may have led to the failure to translate this into a significant between group difference.

7.3.4: Changes in respiratory muscle strength

In line with much of the previously published work there was no evidence of changes in respiratory muscle strength in the current study. Although the hypothesis that the mode of action of NIV is the result of resting of fatigued muscles is superficially appealing, there are few data to support this view. It has not even been shown that COPD patients have clear respiratory muscle weakness, once values have been corrected for the mechanical disadvantage produced by hyperinflation.[57] Furthermore, respiratory muscle fatigue has also not been clearly demonstrated *in vivo*, even in those patients mechanically ventilated within critical care.[247, 303] In summary, the low values of respiratory muscle strength demonstrated in this cohort are likely to be a marker of disease severity and hyperinflation with the failure of these values to change despite the improvement in gas exchange and central respiratory drive leaving little scope

for them to be considered an important mediator of the action of domiciliary NIV in this patient group.

7.3.5: Attenuation of treatment effect during follow up

The majority of physiological studies in this area have involved short term follow up in the most stable patients.[135, 235] Other studies have used a long follow up, again selecting the most stable patients for investigation.[134, 137] The study design, selecting the patients considered to have the potential for most clinical benefit has allowed an assessment of the real physiological treatment effect but has had the unintended consequence of causing significant loss of follow up data due to patient death or severe inter-current illness. In addition to the loss of statistical power at longer follow up there is the potential for a 'survivor' effect, in that those patients from both groups reaching longer follow up may be those with favourable physiological response following the initial insult of a severe hypercapnic exacerbation of COPD.

7.3.6: Conclusion

The use of domiciliary NIV in patients with persistent hypercapnia following an acute exacerbation of COPD is associated with improvement in central respiratory drive which is greater than that achieved with the use of intermittent NIV at the time of decompensated exacerbations only. The treatment also produces a favourable change in daytime resting gas exchange and tidal breathing. Although the confounding effect of both inter-current exacerbations and loss of follow up data may have influenced the precision of the results of the study, the design has allowed a pragmatic assessment of a genuine physiological treatment effect in a high risk patient population that can inform clinical practice.

CHAPTER 8: PHYSIOLOGICAL SUB-STUDY OF THE HOT-HMV TRIAL: EFFECTS OF HOME MECHANICAL VENTILATION ON SLEEP QUALITY AND PHYSICAL ACTIVITY IN PATIENTS WITH HYPERCAPNIC RESPIRATORY FAILURE PERSISTENT POST EXACERBATION OF COPD

8.1: Materials and Methods

The background literature of this study can be found on Page 70 of this thesis. The study utilised patients recruited for the UKCRN multicentre HOT-HMV trial and a full description of the patient recruitment is described earlier in this thesis on Page 76 in the Materials and Methods section. Any deviations from that protocol are provided below.

8.1.1: Subjects

Patients enrolled into the HOT-HMV UK trial were eligible. Four of the sites participated in actigraphy analysis including the Lane Fox Unit, St Thomas' Hospital; Sleep and Ventilation Unit, Royal Brompton Hospital; the Sleep Unit, Leeds University Hospital; and the Ventilation Unit, Aintree University Hospital. Inclusion and exclusion criteria were as detailed in the previous chapter on Page 143 and Page 76.

8.1.2: Trial assessments

Actigraphy

Patients completed a 14 day monitoring period following each assessment, with the exception of the 12 month assessment when the preceding 2 week period was used. The monitoring period included use of an Actiwatch Spectrum (Philips-Respironics, Murrysville, PA, US) with contemporaneous completion of a sleep hygiene diary. The Actiwatch Spectrum device was secured to the non-dominant wrist and patients were asked to wear it throughout the monitoring period with only short breaks for washing and personal hygiene. Sleep periods were set using a combination of activity pattern on actigrams, sleep diary and light sensor readings.

8.1.3: Follow up

Patients underwent follow up assessment at 6 weeks, 3 months, 6 months and 12 months. The study plan with details of all assessments performed at each visit is provided in Table 25.

8.1.4: Data analysis

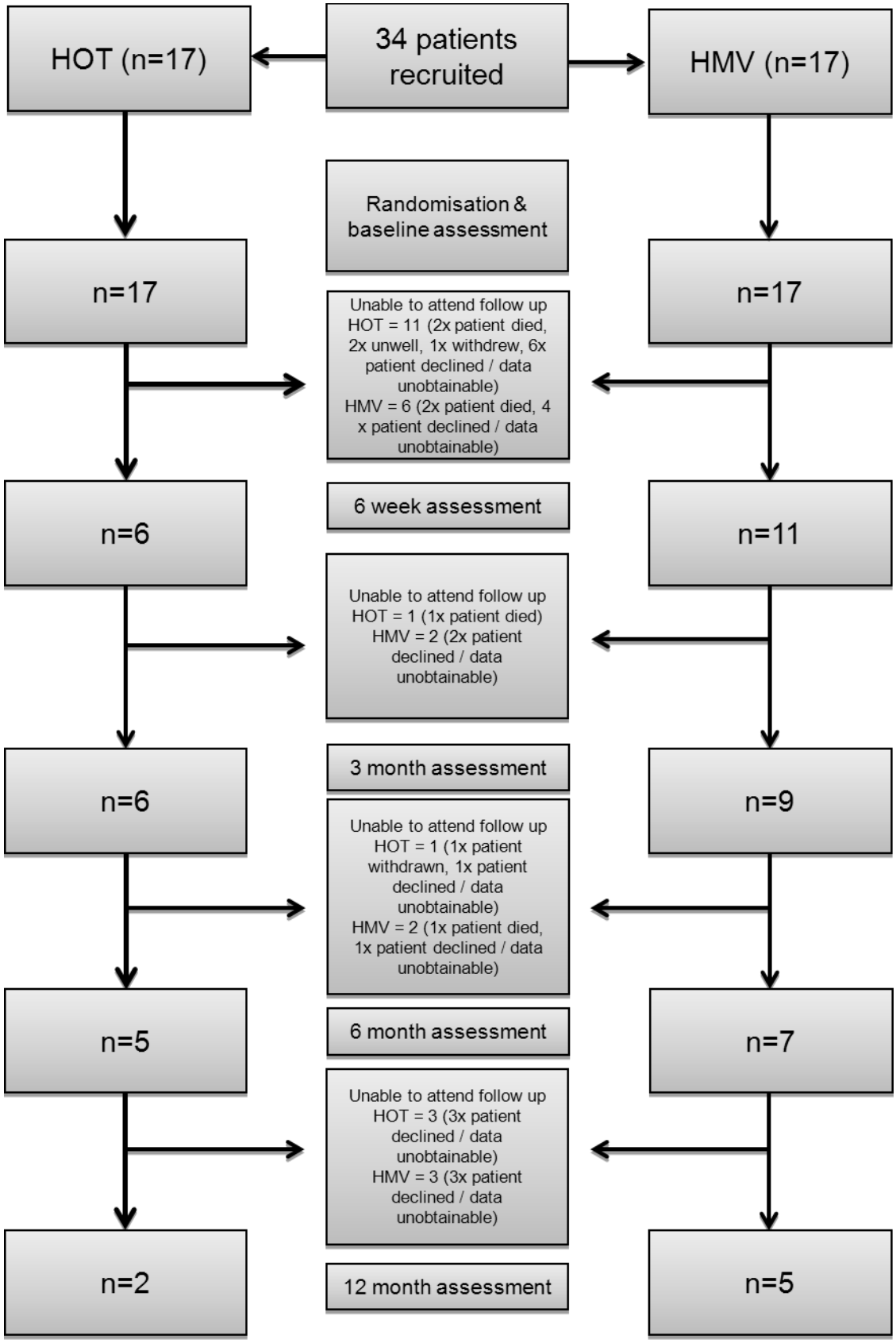
From published data the standard deviation for sleep efficiency in COPD is 10%, therefore a sample size of 60 patients randomised on a 1:1 basis would provide 80% power at the 0.05 significance level to detect a difference in sleep efficiency between groups of 7.5%. This level of difference was chosen as it was considered to be a clinically significant effect that would be perceptible to patients.

8.2: Results

8.2.1: Patient recruitment and baseline measures

34 patients were randomised and completed baseline actigraphy. Recruitment and retention data are provided in Figure 37.

Figure 37: Recruitment and retention for study assessing sleep disruption with high pressure non-invasive ventilation in COPD



Abbreviations: HOT – home oxygen therapy, HMV – home mechanical ventilation.

Despite randomisation and minimisation baseline characteristics of the 2 groups varied with significant between group differences in gender and anthropometric measures (Table 31A and Table 31B). There were no significant differences observed between groups in severity of sleep disordered breathing on oxygen therapy (Table 32).

Table 31: Baseline comparison for randomised patients in actigraphy analysis of sleep disruption of high pressure non-invasive ventilation compared to home oxygen therapy: [A] Anthropometric data and [B] Physiological data

Table 31A: Anthropometric data

		HOT	HMV	p-value
Centre	STH	7	10	
	RBH	5	4	
	AUH	3	2	
	LUH	2	1	
Age (years)		66 ± 11	68 ± 10	0.659
Gender Male / Female*		6/11	12/5	0.039*
BMI (kg/m^2)*		24.6 ± 5.4	20.2 ± 2.8	0.006*
Weight (kg)		66.2 ± 17.4	56.3 ± 10.7	0.053
Fat free mass (kg)		33.0 ± 5.4	31.9 ± 7.3	0.608
Fat free mass index (kg/m^2)		12.3 ± 1.4	11.5 ± 2.4	0.242
Neck circumference (cm)		38 ± 5	36 ± 4	0.161
Waist circumference (cm)*		94 ± 15	85 ± 9	0.047*
Hip circumference (cm)*		99 ± 8	91 ± 6	0.002*

Abbreviations: HOT – home oxygen therapy, HMV – home mechanical ventilation, STH – St Thomas' Hospital, RBH – Royal Brompton Hospital, AUH – Aintree University Hospital, LUH – Leeds University Hospital, BMI – body mass index.

Table 31B: Physiological Data

	HOT	HMV	p-value
Incremental shuttle walk test (m)	91 ± 111	76 ± 85	0.682
$PaCO_2$ on air (kPa)	8.0 ± 0.7	7.9 ± 0.8	0.736
PaO_2 on air (kPa)	6.3 ± 1.1	6.7 ± 1.1	0.393
Bicarbonate on air (mmol/L)	34 ± 3	37 ± 8	0.172
FEV_1 (%)	29 ± 8	24 ± 10	0.121
FVC (%)	62 ± 18	54 ± 29	0.313
FEV_1/FVC	0.38 ± 0.10	0.33 ± 0.07	0.115
TLC (%)[#]	104 ± 18	91 ± 23	0.221
V_a (%)[#]	65 ± 18	71 ± 14	0.568
RV (%)[#]	172 ± 30	135 ± 39	0.056
FRC (%)[#]	149 ± 35	126 ± 31	0.083
DLCO (%)[#]	39 ± 22	26 ± 10	0.210
SRI-SS (/100)	50 ± 13	46 ± 17	0.461
SGRQ-total	67 ± 12	71 ± 14	0.401
MRC (/5)	4 ± 1	5 ± 1	0.060
ESS (/24)	9 ± 5	6 ± 5	0.052

[*]$p<0.05$ between group comparison (independent t-test); [#]performed on HOT=11, HMV=9. Abbreviations: HOT – home oxygen therapy, HMV – home mechanical ventilation, $PaCO_2$ – arterial partial pressure of carbon dioxide, PaO_2 – arterial partial pressure of oxygen, FEV_1 – forced expiratory volume in 1s, FVC – forced vital capacity, TLC – total lung capacity, V_a – alveolar volume, RV – residual volume, FRC – functional residual capacity, DLCO – Diffusion capacity of carbon monoxide, SRI-SS – severe respiratory insufficiency questionnaire summary score, SGRQ-total – St George's respiratory questionnaire total score, MRC – Medical Research Council dyspnoea score, ESS – Epworth sleepiness score.

Similar levels of nocturnal hypoxia and hypercapnia were demonstrated during limited respiratory sleep studies performed on the prescribed oxygen therapy

prior to randomisation (Table 32). There were no cases of significant obstructive sleep apnoea syndrome diagnosed.

Table 32: Comparison of baseline overnight oximetry-capnography performed prior to randomisation in groups subsequently randomised to home oxygen therapy (HOT) and home mechanical ventilation (HMV)

	HOT	**HMV**	p-value
Oxygen prescription ($Lmin^{-1}$)	1 ± 1	1 ± 1	0.573
AHI (/hr)	4 ± 7	10 ± 18	0.399
4%ODI	9 ± 14	9 ± 15	0.963
Mean SpO_2 (%)	89 ± 8	94 ± 4	0.071
Min SpO_2 (%)	69 ± 24	70 ± 16	0.693
%TST SpO_2<90% (%)	34 ± 39	19 ± 24	0.184
Mean $tcCO_2$ (kPa)	8.6 ± 1.1	9.1 ± 1.4	0.294
Max $tcCO_2$ (kPa)	10.3 ± 1.3	10.4 ± 1.8	0.838

Abbreviations: HOT – home oxygen therapy, HMV – home mechanical ventilation, ODI – oxygen desaturation index, SpO_2 – oxyhaemaglobin saturation, TST – total sleep time, $tcCO_2$ – transcutaneous carbon dioxide.

Anthropometric measures as well as daytime $PaCO_2$ and SpO_2 on O_2 therapy correlated with severity of nocturnal hypoxia (Table 33). The severity of nocturnal hypercapnia correlated with daytime $PaCO_2$ performed on room air (mean $tcCO_2$ r=0.489, p=0.004; max $tcCO_2$ r=0.522, p=0.002) but less strongly when performed on prescribed oxygen therapy (mean $tcCO_2$ r=0.250, p=0.161; max $tcCO_2$ r=0.524, p=0.002). There were no significant relationships between anthropometric measures and severity of nocturnal hypercapnia. Finally, there was no relationship demonstrated between spirometry and severity of nocturnal hypoxia or hypercapnia.

Table 33: Correlation between severity of nocturnal hypoxia during treatment with prescribed oxygen therapy and anthropometric measures

	Mean nocturnal SpO_2 (%)		%night time SpO_2<90%	
	r	p value	r	p value
BMI (kg/m^2)	-0.468	0.006	0.313	0.076
Fat free mass (kg)	-0.443	0.010	0.402	0.020
Waist circumference (cm)	-0.383	0.028	0.256	0.151
Neck circumference (cm)	-0.523	0.002	0.535	0.002
$PaCO_2$ on oxygen therapy (kPa)	-0.349	0.047	0.448	0.009
Daytime SpO_2 on oxygen therapy (%)	0.544	0.002	-0.493	0.007

Abbreviations: SpO_2 – oxyhaemaglobin saturation, BMI – body mass index, $PaCO_2$ – arterial partial pressure of carbon dioxide.

8.2.2: Ventilator settings and efficacy of nocturnal non-invasive ventilaiton

12 patients received nocturnal NIV with the Harmony 2 ventilator (Philips-Respironics, Murrysville, PA, US) and 5 patients received nocturnal NIV with the VPAP IIISTa ventilator (ResMed, Bella Vista, Australia). The ventilator settings for patients randomised to home mechanical ventilation in addition to home oxygen therapy were an IPAP 25 ± 2 cmH_2O, EPAP 4 ± 1 cmH_2O, a back-up rate of 14 ± 2 breaths per minute. 15 patients used a full face mask (10 x ComfortFull 2, Philips-Respironics, Murrysville, PA, US; 5 x Mirage Quattro, ResMed, Bella Vista, Australia), 1 patient used a nasal mask (ProfileLite, Philips-Respironics, Murrysville, PA, US) and 1 patient used a total face mask (FitLife, Philips-Respironics, Murrysville, PA, US). As expected, patients randomised to nocturnal NIV had superior control of nocturnal hypoxia and hypercapnia (Table 34).

Table 34: Oximetry-capnography at baseline on allocated treatment

	HOT	**HMV**	p-value
4%ODI	7 ± 13	8 ± 8	0.744

	HOT	HMV	p-value
Mean SpO_2 (%)*	91 ± 6	95 ± 3	0.010*
Min SpO_2 (%)	70 ± 21	80 ± 10	0.115
%TST SpO_2<90% (%)	26 ± 31	9 ± 13	0.053
Mean $tcCO_2$ (kPa)*	8.6 ± 1.0	7.5 ± 1.3	0.010*
Max $tcCO_2$ (kPa)*	10.4 ± 1.2	8.8 ± 1.6	0.003*

*p<0.05 between group comparison (independent t-test). Abbreviations: HOT – home oxygen therapy, HMV – home mechanical ventilation, ODI – oxygen desaturation index, SpO_2 – oxyhaemaglobin saturation, TST – total sleep time, $tcCO_2$ – transcutaneous carbon dioxide.

8.2.3: Exercise capacity and daytime physical activity

Baseline exercise capacity as measured by the incremental shuttle walk test distance correlated with anthropometric measures (weight r=0.425, p=0.014; BMI r=0.371, p=0.034; FFMI r=0.536, p=0.001; FFM r=0.592, p<0.001; waist circumference r=0.463, p=0.007) but there was no relationship observed beween ISWT distance and objective measures of daytime physical activity measured by actigraphy in the week following randomisation (mean activity r=0.238, p=0.182; max activity r=0.289, p=0.103; percentage of day spent mobile r=0.138, p=0.443). The only objective measure of daytime physical activity that correlated with an anthropometric measure was maximum activity count which showed a weak correlation with FFMI (r=0.352, p=0.044). Low levels of activity were present in both groups at baseline with high levels of sedentary behaviour (Table 35). These low levels of activity persisted throughout follow up with no significant change in activity pattern occurring in either group (Figure 38).

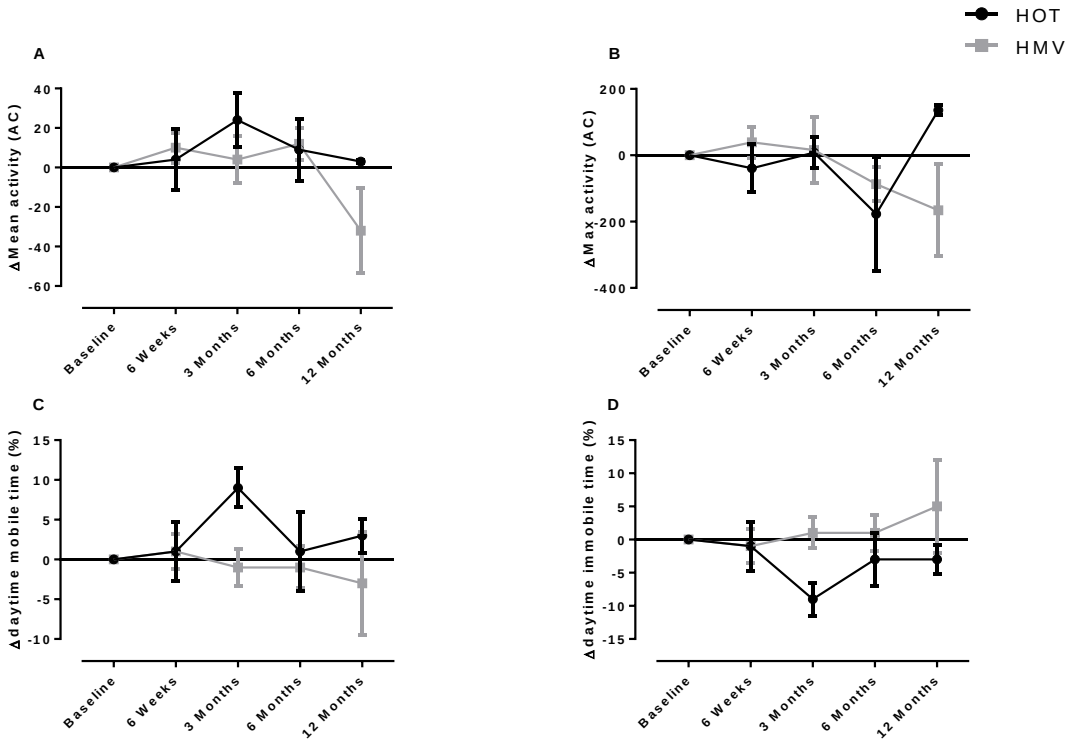
Table 35: Comparison of daytime physical activity in 2 weeks following randomisation between home oxygen therapy (HOT) and home mechanical ventilation (HMV) groups

	HOT	HMV	p-value
Mean activity counts (counts/min)	117 ± 48	113 ± 46	0.797
Max activity counts	882 ± 269	993 ± 293	0.270

	HOT	HMV	p-value
Mobile time (minutes)	639 ± 135	663 ± 124	0.607
%daytime spent mobile (%)	69 ± 15	68 ± 14	0.811
Immobile time (minutes)	292 ± 142	316 ± 142	0.635
%daytime spent immobile (%)	31 ± 14	34 ± 13	0.583

Abbreviations: HOT – home oxygen therapy, HMV – home mechanical ventilation.

Figure 38: Changes in objective measures of physical activity during follow up in home oxygen therapy (HOT) and home mechanical ventilaiton (HMV) groups for [A] mean activity, [B] maximum activity, [C] percentage of daytime period spent mobile and [D] percentage of daytime period spent immobile



Abbreviations: HOT – home oxygen therapy, HMV – home mechanical ventilation.

8.2.4: Differences in actigraphy measured sleep parameters and sleep quality

Analysis of actigraphy data showed similar levels of sleep disruption but demonstrated a significantly longer total sleep time in the HOT group compared to the HMV group (Δ67 min, 95%CI 6 to 127, p=0.032) in the week following

randomisation (Table 36). Sleep efficiency was non-significantly lower in the HMV group at baseline analysis (Δ6%, 95%CI -5 to 18, p=0.279) with no differences in self-reported sleep quality (Table 36).

Table 36: Actigraphy measured sleep parameters in 7 days following randomisation

	HOT	**HMV**	p-value
Sleep efficiency (%)	65 ± 20	58 ± 14	0.279
TST (min)*	322 ± 103	255 ± 67	0.032*
WASO (min)	161 ± 105	153 ± 73	0.814
Sleep latency (min)	12 ± 9	19 ± 29	0.329
Sleep quality	2 ± 1	2 ± 1	0.935

Sleep quality measure on a 3 point scale (1=poor, 2=average, 3=good). Abbreviations: HOT – home oxygen therapy, HMV – home mechanical ventilation, TST – total sleep time, WASO – wake after sleep onset.

Actigraphy analysis of sleep parameters at 6 weeks follow up showed no between group differences in sleep quality or quantity (Table 37). A small, but statistically significant, difference in sleep latency occurred in the HOT group (Δ3 min, 95%CI 0 to 7, p=0.045) with a trend to reduced sleep latency in the HMV group (Δ-13 min, 95%CI -30 to 3, p=0.094).

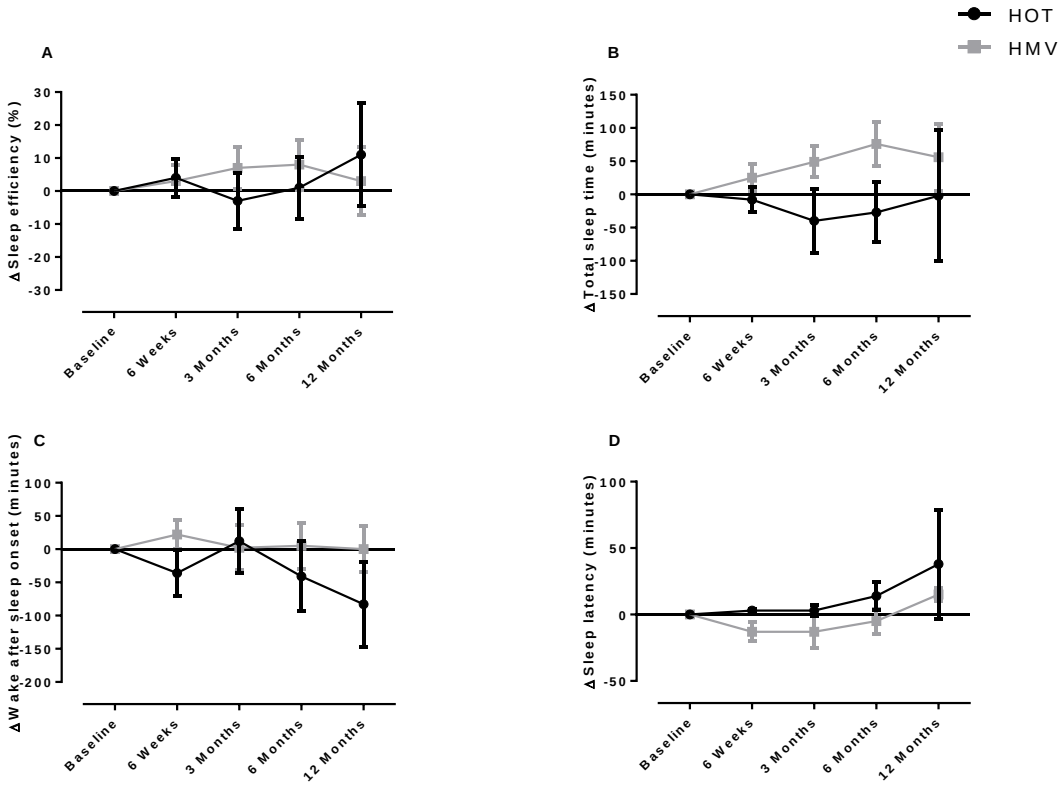
Table 37: Comparison of actigraphy measured sleep parameters in the 2 weeks following 6 week follow up between home oxygen therapy (HOT) (n=6) and home mechanical ventilation (HMV) (n=11) groups

	HOT	**HMV**	Mean difference (95%CI)	p-value
Sleep efficiency (%)	65 ± 17	59 ± 14	6 (-10 to 22)	0.451
TST (min)	304 ± 110	261 ± 67	43 (-48 to 134)	0.330
WASO (min)	151 ± 101	165 ± 77	-15 (-108 to 77)	0.736
Sleep latency (min)	12 ± 7	10 ± 12	2 (-9 to 14)	0.648
Sleep quality	2 ± 1	2 ± 1	0 (-1 to 1)	0.930

Abbreviations: HOT – home oxygen therapy, HMV – home mechanical ventilation, TST – total sleep time, WASO – wake after sleep onset.

Over the duration of longer term follow up (3, 6 and 12 month), there were no significant between group differences observed in either absolute or change from baseline sleep efficiency, TST, WASO or sleep latency (Figure 39), albeit there was a trend to a difference in change in total sleep time and wake after sleep onset.

Figure 39: Comparison of changes in actigraphy measured sleep parameters from baseline to 1 year follow up between treatment groups for [A] sleep efficiency, [B] total sleep time, [C] wake after sleep onset and [D] sleep latency



Abbreviations: HOT – home oxygen therapy, HMV – home mechanical ventilation.

8.2.5: Analysis of sleep data by centre

A higher rate of follow up data loss occurred at peripheral (Aintree University Hospital, Leeds University Hospital) rather than central (St Thomas' Hospital, Royal Brompton Hospital) study sites (data loss at 6 week follow up, Fisher's exact test p=0.003). Baseline comparison shows the groups were similar in terms of anthropometrics, exercise capacity and severity of spirometric deficit

(Table 38). However, despite similar levels of $PaCO_2$ and PaO_2 there were significantly lower bicarbonate levels in the patients recruited from peripheral sites (Δ7 mmol/L, 95%CI 2 to 11, p=0.006).

Table 38: Comparison of patients enrolled in actigraphy sub-study from central or peripheral recruiting sites

	Central sites	Peripheral sites	p-value
Treatment allocation (HOT / HMV)	12/14	5/3	0.419
Age (years)	68 ± 10	65 ± 11	0.583
Gender (Male / Female)	13 / 13	5 / 3	0.536
BMI (kg/m^2)	22 ± 5	23 ± 3	0.772
Fat free mass (kg)	32 ± 7	34 ± 4	0.325
Incremental shuttle walk test (m)	86 ± 109	74 ± 48	0.754
$PaCO_2$ on air (kPa)	8.0 ± 0.8	7.7 ± 0.5	0.312
PaO_2 on air (kPa)	6.6 ± 1.1	6.2 ±1 .1	0.357
Base excess (mmol/L)*	9 ± 3	6 ± 2	0.006*
FEV_1 (%)	26 ± 10	27 ± 8	0.758
FVC (%)	56 ± 25	64 ± 23	0.131
FEV_1/FVC	36	34	0.470

*p<0.05 between group comparison (independent t-test). Abbreviations: HOT – home oxygen therapy, HMV – home mechanical ventilation, BMI – body mass index, $PaCO_2$ – arterial partial pressure of carbon dioxide, PaO_2 – arterial partial pressure of oxygen, FEV_1 – forced expiratory volume in 1s, FVC, forced vital capacity.

Despite the similar baseline characteristics, there were significant differences in sleep and activity patterns in the 2 weeks following randomisation. Patients recruited from peripheral sites had longer sleep times (TST central 274 ± 96 minutes, peripheral 338 ± 55 minutes, Δ-65 minutes, 95%CI -138 to 9 minutes, p=0.081) with significantly lower levels of sleep disruption (WASO central 178 ± 87 minutes, peripheral 89 ± 64 minutes, Δ89 minutes, 95%CI -22 to -157

minutes, p=0.011) translating to significantly higher levels of sleep efficiency (central 57 ± 16%, peripheral 76 ± 12%, ∆19%, 95%CI 7 to 32%, p=0.003). Both groups had similar levels of sleep latency (central sites 15 ± 24 minutes, peripheral 17 ± 11 minutes; p=0.857). Despite poorer sleep quantity and quality patients from the central sites spent a greater proportion of the day mobile (% daytime mobile central 72 ± 11%, peripheral 59 ± 18%, ∆12%, 95%CI 1 to 23, p=0.028) and a lower proportion of the day sedentary (% daytime immobile central 30 ± 12%, peripheral 42 ± 17%, ∆-12%, 95%CI -1 to -23, p=0.031).

8.3: Discussion

8.3.1: Recruitment and data retention

As discussed earlier, with the physiological sub-study the analysis of actigraphy data has been limited by not reaching the pre-specified sample size and by suffering from a larger than expected patient drop-out rate and data loss during follow up. Again, as with the physiological sub-study, inferential statistics have been limited to earlier follow up (baseline to 3 months) but not for longer follow up (6 to 12 months) but all data is quantitatively displayed to fully inform the reader. In addition to the loss of follow up data from patient death and severe inter-current exacerbations there was a loss of follow up data due to technical difficulties. This predominantly occurred in the peripheral centres (Aintree and Leeds) and further contributed to under-powering of this study. This was a consequence of limited manpower for the day to day running of the trial at these peripheral sites, which is a common problem with multicentre trials. Patients from peripheral centres had similar baseline characteristics, but had markedly different sleep and activity profiles in the two weeks following randomisation. Although the reasons for this disparity are unclear, this difference appears independent of body composition or severity of airflow obstruction. If the data analysis is confined to patients recruited from the central sites, there was no effect on the data interpretation. Due to the patient retention issues and loss of data, the difference in total sleep time between home oxygen therapy and home oxygen therapy combined with home mechanical ventilation groups does not achieve significance, but there is a trend towards a difference. The primary endpoint was pre-specified as sleep efficiency at 6 weeks, as it was expected

there may be an acclimatisation effect in the home oxygen therapy and home mechanical ventilation group in the days following NIV setup. All data analysed at this point was from the central sites and in addition to manpower issues for trial delivery at the peripheral sites, there were technical difficulties with the actigraphy software and device failure. Interestingly, there were no reported cases of patient intolerance of the wrist-worn actigraphy device.

8.3.2: Limitations of methods of assessment

Previous data collected of the disruptive effects of nocturnal oxygen therapy and NIV on sleep quality have focussed on the interpretation of single night multichannel polysomongraphy, whilst data for longer term measurement of sleep quality has been lacking. The relative merits of actigraphy and polysomongraphy to measure sleep quality in sleep disordered breathing are discussed earlier in this thesis (page 115). Furthermore, the accuracy of the different physical activity monitoring devices for measuring daytime physical activity, rather than sleep quality, has recently been investigated in COPD patients as part of the European PROActive project (clinicaltrials.gov NCT01388218). Despite the activity count output of the Actiwatch Spectrum device being shown to only moderately correlate with metabolic measures of energy expenditure in severe COPD, it was reliable in detecting a clinically significant improvement in walking speed.[304] This is not unexpected as the Actiwatch Spectrum is a tri-axial accelerometer which quantifies activity counts as a reflection of change in speed and does not measure energy expenditure.

8.3.3: Actigraphy assessed sleep disruption

The primary outcome of the study was to investigate sleep quality at 6 weeks. As already discussed, the study was underpowered to confidently exclude a significant difference in sleep efficiency at this time point. However, the longitudinal nature of the data collected allows for meaningful analysis of the effect of home mechanical ventilation in addition to home oxygen therapy on sleep quality in severe COPD complicated by hypercapnic respiratory failure. There appears a significant effect of home mechanical ventilation on sleep quantity and objective sleep quality in period immediately following home mechanical ventilation setup. However, this effect did not significantly impair subjective sleep quality and the between group difference consistently narrowed

during the study follow up. This has important implications for interpreting the other published data. The work by Dreher *et al* investigated sleep quality, using multichannel polysomnography, comparing a high and low intensity non-invasive ventilation approach, albeit in patients already established on a high intensity (high pressure and high back up rate) non-invasive ventilation.[142] The current data supports the view that these patients were already acclimatised to the treatment and thus the findings may not reflect those observed in a group of COPD patients naïve to non-invasive ventilation. It could be inferred that sleep disruption in high and low intensity non-invasive ventilation may relate to the device and interface issues rather than the ventilatory settings and so both strategies may induce sleep disruption initially following non-invasive ventilation setup. These data are clinically useful; the clinician can inform the patient that although they may have an initial deterioration in both sleep quantity and quality, this negative effect is short lived.

8.3.4: Control of nocturnal hypoventilation

Earlier work has shown a clear relationship between nocturnal hypoventilation and daytime resting gas exchange and anthropometric measures in patients with less severe chronic hypercapnic respiratory failure (mean $PaCO_2$ 6.5 ± 0.9 kPa) who were not on LTOT.[305] De Angelis *et al* investigated the relationships between nocturnal oximetry and anthropometrics, spirometry and daytime gas exchange. The patients studied by De Angelis and colleagues were of a similar age (65.2 ± 8.1 years) with slightly higher BMI (26.1 ± 2.7) and a less severe phenotype in terms of spirometry and gas exchange when compared to the current study (FEV_1 43 ± 15%, PaO_2 9.1 ± 0.8 kPa, $PaCO_2$ 6.5 ± 0.9 kPa). The De Angelis study protocol performed nocturnal oximetry on air rather than on oxygen therapy as was the protocol in HOT-HMV UK. However a similar inverse relationship was demonstrated between mean nocturnal SpO_2 and body mass index (De Angelis *et al* $r=-0.452$, $p<0.01$; HOT-HMV $r=-0.468$, $p=0.006$).[305] The degree of correlation between mean nocturnal SpO_2 and body mass index was significant in the data reported by De Angelis *et al* and the current data presented in this thesis in patients with mild to severe chronic hypercapnic respiratory failure, whereas the relationship has been shown to be weak in COPD patients without chronic hypercapnic respiratory failure ($r=-0.26$,

$p<0.02$).[306] Interestingly, there was no relationship between body mass index and measures of nocturnal hypercapnia (mean $tcCO_2$ $p=0.817$, max $tcCO_2$ $p=0.721$) indicating that patients suffering from COPD and OSA overlap had been successful excluded from the HOT-HMV trial cohort. The finding in the current study of strong relationships between daytime $PaCO_2$ and SpO_2 on oxygen therapy and nocturnal hypoxia is in disagreement with earlier data supporting a relationship with hypercapnia, but not daytime arterial partial pressure of oxygen.[306] However, differences in the patient population are responsible, in part, for this observation. The earlier work by Chaouat *et al* investigated nocturnal desaturations in patients without established hypoxic respiratory failure (PaO_2 >7.3 kPa) and these patients will be positioned on the more favourable portion of the oxyhaemoglobin dissociation curve and as such SpO_2 will be less affected by small changes in PaO_2 occurring due to sleep hypoventilation than patients with more severe hypoxic respiratory failure.[306] Whilst it is unsurprising that measures of daytime gas exchange on oxygen therapy correlate with the severity of nocturnal hypoxia and hypercapnia on the same flow rate level of oxygen therapy, the similarity in the strength of relationship with body mass index is perhaps unexpected given the different severity of the patient groups.

Many of the previous published clinical trials reporting the limited effect of home mechanical ventilation in COPD patients have been criticised for their failure to improve daytime gas exchange.[93, 140] This has largely been attributed to the low airway pressures delivered by the non-invasive ventilator used and the failure to clearly demonstrate an improvement in nocturnal hypoventilation. Meecham-Jones *et al* demonstrated the importance of the control of nocturnal hypoventilation in a small randomised crossover study that showed a direct correlation between the change in nocturnal $tcCO_2$ and improved daytime $PaCO_2$.[136] The group in this trial had similar severity of nocturnal hypoxia and hypercapnia on oxygen therapy alone but the home mechanical ventilation group showed a significant improvement following initiation of nocturnal non-invasive ventilation. Patients allocated to home mechanical ventilation also had enhanced control of nocturnal hypoxia and hypercapnia than patients allocated to home oxygen therapy alone. This study allowed for the true effect of

nocturnal non-invasive therapy, administered with adequate ventilator pressure, to control nocturnal hypoventilation rather than sub-therapeutic home mechanical ventilation and therefore address some of the concerns regarding interpretation of the data raised by earlier trials. As researchers involved in clinical trials, we need to distinguish between the failure of intervention to provide clinical benefit and the failure of an intervention to be delivered effectively as the outcome will be the same.

8.3.5: Physical activity and exercise capacity

Patients in the home oxygen therapy group and home mechanical ventilation in addition to home oxygen therapy group had profoundly low levels of physical activity in the two weeks following randomisation with activity levels in both groups being lower than those observed in patients following hospital admission for an acute exacerbation of COPD that was not complicated by acute on chronic respiratory failure requiring acute non-invasive ventilation.[307] This low level of activity did not significantly alter in either group throughout the duration of follow up. This is in contrast to previous data showing improved levels of physical activity at 1 month follow up compared to immediately following hospital discharge.[109] The data reported by Pitta *et al* was collected on a similar sized patient group (n=17) with a similar degree of airflow limitation (FEV_1 29% (20-48)) but without chronic respiratory failure. The presence of respiratory failure is an established poor prognostic feature in COPD and is associated with increased morbidity including high rates of hospital readmission.[147] Whilst Pitta *et al* showed an increase in walking time at one month following an acute exacerbation requiring hospitalisation, they also demonstrated that there were only modest, non-significant, improvements in other measures of physical activity (time spent standing, sitting, lying down or in weight bearing activity) and that those patients with less improvement at follow up were at higher risk of subsequent readmission. It is rational to propose that the failure of activity to improve during recovery following an acute exacerbation is correlated to the severity of the cohort enrolled in our study. Exercise capacity correlated with a range of anthropometric measures, most notably fat free mass and fat free mass index. Both these measures of lean body mass have been shown previously to be strong predictors of quadriceps strength in COPD.[308] Although

quadriceps force was not directly measured in this patient cohort it is established that lean body mass and quadriceps strength also correlate with exercise capacity in COPD.[309] Earlier studies have demonstrated a relationship between physical activity and exercise capacity in large cohorts of COPD patients covering all GOLD stages.[97] However, this relationship may vary with disease severity with recent data suggesting that whilst quadriceps strength is an important determinant of physical activity in early disease (GOLD stage I), it is the degree of airway flow limitation and hyperinflation during standard lung function testing rather than peripheral muscle weakness that dictates physical activity in more severe disease (GOLD IV).[310] This may explain, in part, the apparent discord between the results detailed in this thesis from a select group of GOLD stage IV patients with hypercapnic respiratory failure and larger cohorts of patients that cover a complete cross-section of disease severity.

8.3.6: Variation in sleep and activity by trial site

Despite patients from the central and peripheral sites having similar clinical and anthropometric features there were pronounced differences in the sleep and activity characteristics collected in this study. The only statistically significant difference in baseline features was a higher base excess in the central cohort, this was accompanied by a non-significantly higher $PaCO_2$. This could be interpreted as a chance finding or suggesting that with larger numbers in the cohort the central group may have been shown to have more severe hypercapnic respiratory failure. Given this clinical trend it is therefore perhaps surprising that the central group had higher levels of daytime activity as measured by percentage of daytime spent mobile. All of the sites involved in the study serve urban environments and thus the reason for this apparent discord is unclear. London has high levels of migration and so one could hypothesise that patients in London may have less well established support networks and therefore are required to perform more activities of daily living than patients outside of London. Despite the higher level of activity observed in the central cohort there was no statistically significant difference in the exercise capacity, as measured by incremental shuttle walk test, between groups. More pronounced than the activity differences were the differences in actigraphy measured sleep parameters with patients outside of London achieving an extra

hours sleep per night than there comparators in the central cohort. This improvement in sleep quantity was accompanied by an improvement in sleep quality with reduced sleep disruption and higher sleep efficiency in the peripheral cohort. The reasons for this difference are not explained by the anthropometric or clinical characteristics of the patients and again it raise the possibility of the patients from outside of the central sites being phenotypically different to those from central sites. Another potential explanation is that the difference has occurred due to the reduced data collection rates at the peripheral centres and that this has selected out a sleepier, less active cohort that the larger central cohort, although why these characteristics would have led you to be more likely to complete the actigraphy component of the study is not clear.

8.3.7: Conclusion

The study was unable to demonstrate a negative effect of home mechanical ventilation on actigraphy measured parameters of sleep quality and quantity 6 weeks following initiation of home mechanical ventilation. However, it cannot be concluded that there is no significant effect as poor recruitment means the study was underpowered to assess the primary outcome. The study remains informative as it shows impairment in sleep quantity immediately following initiation of home mechanical ventilation that attenuates during follow up.

CHAPTER 9: DISCUSSION OF THE PHYSIOLOGICAL ASSESSMENT OF THE RESPIRATORY LOAD-CAPACITY-DRIVE RELATIONSHIP IN RESPIRATORY FAILURE

9.1: Physiological and clinical outcomes following HMV in the treatment of obesity hypoventilation syndrome

The data presented in this thesis demonstrates the clinical importance of physiologically targeted ventilator setup. The previous studies, indicating a superior control of nocturnal hypoventilation could be achieved when using volume targeted NIV were shown to be a result of study design rather than ventilator technology. The study demonstrated the importance of targeting the setup of HMV to overnight physiological monitoring to ensure the abolition of upper airways obstruction and the amelioration of nocturnal hypoventilation, as measured by $tcCO_2$. The implementation of this strategy provided similar levels of delivered pressure support in both patients randomised to usual as opposed to volume targeted NIV. Of equal importance was demonstrating that all of the important clinical and physiological parameters correlate to improvement in respiratory failure, as measured by daytime $PaCO_2$. This confirms current clinical practice and again stresses the importance of ensuring ventilator setup strategy is implemented in order to control sleep disordered breathing. The study is the first to show a therapeutic effect of HMV on objective physical activity in OHS, a finding that warrants further evaluation given the importance of this endpoint in the underlying aetiology of obesity.

9.2: A novel marker of neural respiratory drive to assess clinical change during exacerbations of COPD

The data collected as part of this thesis has demonstrated the potential clinical utility of a novel physiological biomarker of clinical change during acute exacerbations of COPD. $EMG_{para\%max}$ has been shown to have acceptable levels of reproducibility in stable disease and to accurate reflect response to treatment during hospitalised exacerbations of COPD. This novel physiological assessment tool outperformed routine clinical and physiological parameters with

receiver operating curve analysis suggesting the discriminatory power of the test met clinically useful benchmarks. In addition to the accurate monitoring of clinical course during an exacerbation, the failure of NRD, as reflected by $EMG_{para\%max}$, to reduce between admission and discharge was associated with a significantly higher risk of readmission in the subsequent 14 days. The ability to risk stratify patients at discharge for risk of subsequent readmission represent a potential advance in clinical care, which requires further evaluation in larger studies and in the primary care population.

To move this novel physiological test into routine clinical practice would face a number of challenges. There are basic technological issues of translating a research assessment delivered by a highly trained operator into a standard test that can be delivered by nursing or allied health professional staff. If a robust and simple equipment protocol could be developed and staff trained there would still be a need to demonstrate unequivocal superiority of the use of neural respiratory drive over the routine clinical parameters. Furthermore, the clinical benefit would need to provide a sufficient cost saving to justify the outlay on equipment and training. Also the development and implementation of the NHS early warning score has advocated the use of a standardised dataset across the health service for the assessment of the unwell patient thus use of a neural respirator drive would need to be integrated alongside as a disease specific adjunct.[311] A purported benefit of the NHS early waning score is that the same variables will be collected on different wards or hospitals facilitating training and making threshold triggering easier to implement. The addition of disease specific markers such as neural respiratory drive will need to be carefully thought through to ensure that they do not detract from other aspects of patient assessment systems.

9.3: Physiological changes in the load-capacity drive relationship following HMV in the treatment of hypercapnic COPD

The data presented represents the first use of a randomised controlled trial design to evaluate the physiological action of HMV in hypercapnic COPD. The

data indicates the improvement in gas exchange produced by HMV is mediated principally through changes in central respiratory drive and tidal breathing pattern. Poor recruitment prevented a definitive evaluation of changes in respiratory muscle load although the trends were supportive of the previous data suggesting a lowering of threshold load. In line with existing data there were no significant changes to respiratory muscle capacity following HMV.

The serial measurements of respiratory drive in patients with recent use of NIV for an acute decompensated episode of hypercapnic respiratory failure allowed for a useful observation; the attenuation in central drive in patients on home oxygen therapy alone. There is an acknowledged high readmission and mortality rate in patients who have survived an admission for an acute exacerbation of COPD complicated by decompensated hypercapnic respiratory failure with much of the morbidity and mortality happening within the first few weeks following discharge.[148, 149] The rapid diminution of central respiratory drive by 6 weeks that occurred in the control group may in part explain this with patients less well able to respond to increases in CO_2 that may occur with a repeat exacerbation. This is encouraging for the clinical outcomes of the HOT HMV UK study that are currently awaited.

9.4: Physiological and clinical outcomes following HMV in the treatment of hypercapnic COPD

The use of a high pressure ventilatory strategy allowed significant improvement of nocturnal sleep disordered breathing without a demonstrable deleterious effect on either subjective or objective sleep quality. There was, however, a significant if short term effect on sleep quality with the addition of HMV to HOT. Despite improvements in respiratory failure in the HMV group there was no significant effect on physical activity. The study highlights the severe limitation to physical activity in these severe COPD patients and the minimal impact of home mechanical ventilation on this outcome. The reasons for this may relate to the severity of the disease population studied but warrants further investigation to identify strategies, such as home rehabilitation, that could bring improvements in this important area. The trial design did not include baseline pulmonary rehabilitation in all patients and recent data has suggested that

domiciliary NIV may augment the response of hypercapnic patients to rehabilitation.[111] The failure of NIV to improve physical activity may relate to the severity of the phenotype chosen or the lack of a specific pulmonary rehabilitation element.

9.5: Future work

9.5.1: Obesity related respiratory failure

The work described earlier in this thesis demonstrates the equivalence of gold standard care, a nurse led protocolised titration of NIV, compared to an automated titrating device in the management of obesity hypoventilation syndrome. Due to the increasing obesity epidemic, OHS will become an ever more common indication for domiciliary NIV and the results of this study raise the possibility of using home setup with advanced ventilators to achieve optimum personalised NIV settings. This has the advantage of not necessitating a prolonged hospital admission for all patients allowing a potential cost saving.

9.5.2: Parasternal EMG measurement

The data collected using EMG_{para} has demonstrated that the measurement of neural respiratory drive is feasible in acute hospital admissions and may provide clinically useful information. A larger prospective study is required to confirm the pilot study findings and confirm the threshold levels that would allow patients to be categorised as high or low risk of readmission. Further work may include a multi-centre cluster randomised study to identify whether the additional information provided by the measurement of neural respiratory drive to risk stratify patients presenting with acute exacerbations of COPD translated into reduced hospital readmissions, hospital length of stay and mortality. The use of neural respiratory drive to assess patient response to treatment in other respiratory disorders is also a potential avenue for further research. Most appealing would be asthma that is also characterised by hyperinflation that augments the activity of the upper parasternal muscles but there is also the potential to use neural respiratory drive in critical care to assist with weaning and to assess patient-ventilator synchrony.

9.5.3: HOT-HMV UK

The lower than anticipated rates of recruitment means that this work is continuing and should either demonstrate or refute the clinical utility of domiciliary NIV in hypercapnic COPD following an acute hypercapnic exacerbation.

CHAPTER 10: PUBLICATIONS ARRISING FROM THIS THESIS

10.1: Peer Reviewed Primary Research Papers

Murphy PB, Kumar A, Reilly C, Jolley C, Walterspacher S, Fedele F, Hopkinson NS, Man WD, Polkey MI, Moxham J, Hart N. Neural respiratory drive as a physiological biomarker to monitor change during acute exacerbations of COPD. Thorax 2011;66:602-8.

Murphy PB, Davidson C, Hind MD, Simonds A, Williams AJ, Hopkinson NS, Moxham J, Polkey M, Hart N. Volume targeted versus pressure support non-invasive ventilation in patients with super obesity and chronic respiratory failure: a randomised controlled trial. Thorax 2012;67:727-34.

10.2: Abstracts

2011

Murphy PB, Moxham J, Polkey MI, Hart. UK HOT-HMV Trial: Acceptability and tolerability of high pressure domiciliary non-invasive ventilation (NIV) in COPD. Thorax 2011;66:Suppl 4 A55.

Murphy PB, Moxham J, Polkey MI, Hart N. HOT-HMV UK: An investigation into mechanisms of action of home mechanical ventilation (HMV) following acute hypercapnic exacerbations of COPD. Eur Respir J 2011;38:Suppl 55 255s**.**

Murphy PB, Davidson AC, Williams AJ, Simonds A, Hind M, Moxham J, Polkey MI, Hart N. Interim Data From A Randomised Controlled Trial Of Average Volume-Assured Pressure Support (AVAPS) Versus Spontaneous-Timed (ST) Pressure Support In Obesity Hypoventilation Syndrome (OHS). Am J Respir Crit Care Med 183;2011:A6236.

2010

Murphy PB, Gibson GJ, Polkey MI, Hart N. HOT-HMV UK: prevalence of persistent significant hypercapnia following acute exacerbation of COPD (AECOPD) requiring non-invasive ventilation (NIV). Thorax 2010;65:Suppl 4 A33.

Murphy PB, Polkey MI, Hart N. HOT-HMV UK: sleep disruption following initiation of domiciliary NIV in hypercapnic COPD. Thorax 2010;65:Suppl 4 A145.

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Murphy PB, Williams A, Davidson AC, Simonds A, Hind M, Polkey MI, Hart N. Investigating patient dependence on back up rate pressure controlled ventilation (PCV) in obesity hypoventilation syndrome (OHS). Eur Respir J 2010;36:Suppl 54 655s.

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Murphy PB, Davidson AC, Williams A, Hind M, Simonds A, Polkey MI, Hart N. Levels Of Physical Activity Improve After Initiation Of Non-invasive Ventilation (NIV) In Obesity Related Respiratory Failure (ORRF). Am J Respir Crit Care Med 2010;181:A2241.

2009

Murphy PB, Brignall K, Hind M, Simonds A, Davidson AC, Williams A, Moxham J, Polkey MI, Hart N. Activity levels at initiation of Home Mechanical Ventilation in Obesity Hypoventilation Syndrome. Thorax 2009;64:Suppl 4 A29.

Murphy PB, Kumar A, Reilly C, Jolley C, Brignall K, Polkey MI, Moxham J, Hart N Clinical usefulness of measuring neural respiratory drive for identification of deterioration in acute exacerbations of COPD. Thorax 2009;64:Suppl 4 A43.

Murphy PB, Brignall K, Williams AJ, Davidson AC, Hind M, Simonds A, Moxham J, Polkey MI, Hart N. Health Related Quality of Life in Obesity Hypoventilation Syndrome (OHS) at initiation of Home Mechanical Ventilation (HMV). Thorax 2009; 64:Suppl 4 A137.

Murphy PB, Kumar A, Marie Z, Reilly C, Jolley C, Polkey MI, Moxham J, Hart N. Measuring EMG_{para} in patients with COPD. Eur Respir J 2009:34:Suppl 53 814s.

Murphy PB, Hind M, Simonds A, Williams A, Davidson AC, Polkey MI, Hart N. Health related quality of life in OHS. Eur Respir J 2009:34:Suppl 53 130s.

10.3: Other Peer Reviewed Publications

10.3.1: Original peer-reviewed papers

Connolly BA, Jones GD, Curtis AA, **Murphy PB**, Douiri A, Hopkinson NS, Polkey MI, Moxham J, Hart N. Clinical predictive value of manual muscle strength testing during critical illness: an observational cohort study. Critical Care. 2013;17(5):R229

Murphy PB, Brignall K, Moxham J, Polkey MI, Davidson AC, Hart N. High pressure vs high intensity non-invasive ventilation in stable hypercapnic COPD: A randomised crossover trial. Int J COPD 2012;7:811-8.

10.3.2: Letters, editorials and reviews

Murphy PB, Hart N. Who benefits from home mechanical ventilation? Clinical Medicine 2009;9:160-163.

Murphy PB, Lyall R, Hart N, Polkey MI. Assessment of respiratory muscle strength in MND; is asking enough? European Respiratory Journal 2010;35:245-246.

Murphy PB, Polkey MI, Hart N. Obesity hypoventilation syndrome: The need for a multifaceted approach to treatment. Chest 2012;142:540-1.

Murphy PB, Brignal K, Moxham J, Polkey MI, Davidson AC, Hart N. Author's reply: High pressure versus high intensity noninvasive ventilation in stable

hypercapnic chronic obstructive pulmonary disease: a randomized crossover trial. Int J COPD. 2013;8:257-8.

10.3.3: Book chapters

Murphy PB, Polkey MI, Hart N. Diagnostic tests in the assessment of patients for home mechanical ventilation. Non-invasive Ventilation and Weaning: Principles and Practice. *Eds* Elliott MW, Nava S, Schonhofer B. Hodder Arnold 2010.

Murphy PB, Hart N. Advances in acute non-invasive ventilation: translating clinical trials into clinical practice. Horizons in Medicine vol. 22. Royal College of Physicians 2010.

10.3.4: Abstracts

Khatun Y, **Murphy PB**, Davidson AC, Hart N. Seasonal variation in initiation and discontinuation of domiciliary non-invasive ventilation: a 12-month cohort study. Thorax 2011;66:Suppl 4 A179-A180.

Ramsay MC, Suh E-S, Mandal S, **Murphy PB**, Steier J, Simonds A, Hart N. The effect of posture on the 2nd intercostal space surface parasternal electromyogram (EMG_{para}): validating a novel clinical tool to measure neural respiratory drive. Thorax 2011;66:Suppl 4 A53.

Suh E-S, Ramsay MC, Mandal S, Boleat E, Christian B, Henderson K, **Murphy PB**, Moxham J, Hart N.Parasternal muscle electromyelography (EMG_{para}) reflects observed changes in dynamic hyperinflation during acute exacerbations of chronic obstructive pulmonary disease (AECOPD) Thorax 2011;66:Suppl A53-A54.

Connolly B, Curtis A, Jones G, **Murphy PB**, Moxham J, Hart N. Clinical predictive value of the medical research council sumscore in critically ill patients. Thorax 2011;66:Suppl 4 A95.

Murphy PB, Dillon R, Williams AJ, Howard J, Hart N. A pilot study of the prevalence of sleep disordered breathing (SDB) and nocturnal hypoxia in symptomatic adults with Sickle Cell Disease (SCD) and its relationship with disease severity. Thorax 2010;65:Suppl 4 A11.

Lee KK, Suh E-S, Peisch J, McGlone A, Mistry A, **Murphy PB**, Williams AJ, Davidson AC, Hart N. Phenotypic differences between obese patients with eucapnic and hypercapnic sleep-disordered breathing (SDB). Thorax 2010;65:Suppl 4 A32.

Brignall KA, **Murphy PB**, Moxham J, Polkey MI, Davidson AC, Hart N. A randomised crossover trial of pressure support ventilation (PSV) versus pressure controlled ventilation (PCV) in stable hypercapnic Chronic Obstructive Pulmonary Disease (COPD). Thorax 2010;65:Suppl 4 A31-A32.

Shrikrishna D, Kelly J, Coissi G, **Murphy PB**, Puthucheary ZA, Seymour JM, Hart N, Moxham J, Polkey MI, Hopkinson N. Physical activity is associated with ultrasound measurement of rectus femoris cross-sectional area and quadriceps strength independent of FEV1 in COPD. Eur Respir J 2010;36:Suppl 54 723s.

Brignall K, Utterson M, **Murphy PB**, Semeganda R, Mackie M, Weston N, Scaffardi A, Davidson AC, Hart N. Clinical evaluation of patient ventilator asynchrony (PVA) in patients with chronic respiratory failure receiving home mechanical ventilation (HMV). Eur Respir J 2010;36:Suppl 54 772s.

Murphy PB, Dillon R, Higgins S, Brignall K, Williams AJ, Davidson AC, Howard J, Hart N. Prevalence of symptomatic obstructive sleep apnoea and nocturnal hypoxic load in adult sickle cell disease. Thorax 2009;64:Suppl 4 A140.

Murphy PB, Jayasooriya N, Lumgair H, Ondhia C, Grey N, Davidson AC, Mackie M, Williams AJ, Hart N. Mortality in obesity related respiratory failure. Eur Respir J 2009:34:Suppl 53 33s.

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Appendix A: SGRQ

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE
ORIGINAL ENGLISH VERSION

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE (SGRQ)

This questionnaire is designed to help us learn much more about how your breathing is troubling you and how it affects your life. We are using it to find out which aspects of your illness cause you most problems, rather than what the doctors and nurses think your problems are.

Please read the instructions carefully and ask if you do not understand anything. Do not spend too long deciding about your answers.

Before completing the rest of the questionnaire:

Please tick in one box to show how you describe your current health:

Very good	Good	Fair	Poor	Very poor
☐	☐	☐	☐	☐

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continued…

St. George's Respiratory Questionnaire
PART 1

Questions about how much chest trouble you have had over the past 3 months.

Please tick (✓) *one box for each question*:

	most days a week	several days a week	a few days a month	only with chest infections	not at all
1. Over the past 3 months, I have coughed:	☐	☐	☐	☐	☐
2. Over the past 3 months, I have brought up phlegm (sputum):	☐	☐	☐	☐	☐
3. Over the past 3 months, I have had shortness of breath:	☐	☐	☐	☐	☐
4. Over the past 3 months, I have had attacks of wheezing:	☐	☐	☐	☐	☐

5. During the past 3 months how many severe or very unpleasant attacks of chest trouble have you had?

Please tick (✓) *one*:

- more than 3 attacks ☐
- 3 attacks ☐
- 2 attacks ☐
- 1 attack ☐
- no attacks ☐

6. How long did the worst attack of chest trouble last?
(Go to question 7 if you had no severe attacks)

Please tick (✓) *one*:

- a week or more ☐
- 3 or more days ☐
- 1 or 2 days ☐
- less than a day ☐

7. Over the past 3 months, in an average week, how many good days (with little chest trouble) have you had?

Please tick (✓) *one*:

- No good days ☐
- 1 or 2 good days ☐
- 3 or 4 good days ☐
- nearly every day is good ☐
- every day is good ☐

8. If you have a wheeze, is it worse in the morning?

Please tick (✓) *one*:

- No ☐
- Yes ☐

St. George's Respiratory Questionnaire
PART 2

Section 1

How would you describe your chest condition?

Please tick (✓) *one*:

- The most important problem I have ☐
- Causes me quite a lot of problems ☐
- Causes me a few problems ☐
- Causes no problem ☐

If you have ever had paid employment.

Please tick (✓) *one*:

- My chest trouble made me stop work altogether ☐
- My chest trouble interferes with my work or made me change my work ☐
- My chest trouble does not affect my work ☐

Section 2

Questions about what activities usually make you feel breathless <u>these days</u>.

Please tick (✓) in ***each box*** that applies to you ***these days***:

	True	False
Sitting or lying still	☐	☐
Getting washed or dressed	☐	☐
Walking around the home	☐	☐
Walking outside on the level	☐	☐
Walking up a flight of stairs	☐	☐
Walking up hills	☐	☐
Playing sports or games	☐	☐

continued...

St. George's Respiratory Questionnaire
PART 2

Section 3

Some more questions about your cough and breathlessness <u>these days</u>.

	Please tick (✓) in ***each box*** that applies to you ***these days***: True	False
My cough hurts	☐	☐
My cough makes me tired	☐	☐
I am breathless when I talk	☐	☐
I am breathless when I bend over	☐	☐
My cough or breathing disturbs my sleep	☐	☐
I get exhausted easily	☐	☐

Section 4

Questions about other effects that your chest trouble may have on you <u>these days</u>.

	Please tick (✓) in ***each box*** that applies to you ***these days***: True	False
My cough or breathing is embarrassing in public	☐	☐
My chest trouble is a nuisance to my family, friends or neighbours	☐	☐
I get afraid or panic when I cannot get my breath	☐	☐
I feel that I am not in control of my chest problem	☐	☐
I do not expect my chest to get any better	☐	☐
I have become frail or an invalid because of my chest	☐	☐
Exercise is not safe for me	☐	☐
Everything seems too much of an effort	☐	☐

Section 5

Questions about your medication, if you are receiving no medication go straight to section 6.

	Please tick (✓) in ***each box*** that applies to you ***these days***: True	False
My medication does not help me very much	☐	☐
I get embarrassed using my medication in public	☐	☐
I have unpleasant side effects from my medication	☐	☐
My medication interferes with my life a lot	☐	☐

St. George's Respiratory Questionnaire
PART 2

Section 6

These are questions about how your activities might be affected by your breathing.

Please tick (✓) in ***each box*** that applies to you ***because of your breathing***:

	True	False
I take a long time to get washed or dressed	☐	☐
I cannot take a bath or shower, or I take a long time	☐	☐
I walk slower than other people, or I stop for rests	☐	☐
Jobs such as housework take a long time, or I have to stop for rests	☐	☐
If I walk up one flight of stairs, I have to go slowly or stop	☐	☐
If I hurry or walk fast, I have to stop or slow down	☐	☐
My breathing makes it difficult to do things such as walk up hills, carrying things up stairs, light gardening such as weeding, dance, play bowls or play golf	☐	☐
My breathing makes it difficult to do things such as carry heavy loads, dig the garden or shovel snow, jog or walk at 5 miles per hour, play tennis or swim	☐	☐
My breathing makes it difficult to do things such as very heavy manual work, run, cycle, swim fast or play competitive sports	☐	☐

Section 7

We would like to know how your chest <u>usually</u> affects your daily life.

Please tick (✓) in ***each box*** that applies to you ***because of your chest trouble***:

	True	False
I cannot play sports or games	☐	☐
I cannot go out for entertainment or recreation	☐	☐
I cannot go out of the house to do the shopping	☐	☐
I cannot do housework	☐	☐
I cannot move far from my bed or chair	☐	☐

continued...

St. George's Respiratory Questionnaire

Here is a list of other activities that your chest trouble may prevent you doing. (You do not have to tick these, they are just to remind you of ways in which your breathlessness may affect you):

Going for walks or walking the dog

Doing things at home or in the garden

Sexual intercourse

Going out to church, pub, club or place of entertainment

Going out in bad weather or into smoky rooms

Visiting family or friends or playing with children

Please write in any other important activities that your chest trouble may stop you doing:

.....

.....

.....

.....

Now would you tick in the box (one only) which you think best describes how your chest affects you:

It does not stop me doing anything I would like to do ☐

It stops me doing one or two things I would like to do ☐

It stops me doing most of the things I would like to do ☐

It stops me doing everything I would like to do ☐

Thank you for filling in this questionnaire. Before you finish would you please check to see that you have answered all the questions.

Appendix B: SRI questionnaire

Severe Respiratory Insufficiency Questionnaire

SRI

General Health Questionnaire for patients with Severe Respiratory Insufficiency

Dear patient!

We are treating you for your respiratory disorder. Please fill in this questionnaire so that we can assess your current state of general health. Please answer every question by marking the appropriate answer once with a cross. Participation is, of course, voluntary. All data is bound by the rules of patient/doctor confidentiality and will be treated in strict confidence. Your attending physician will be pleased to answer any questions you may have.

Code number:

SRI

The following question relate to your general condition. You will see statements related to various aspects of daily life.

How did you feel ***last week?*** For EVERY statement please mark the answer that best applies to you.

	completely untrue - 2	mostly untrue - 1	sometimes true 0	mostly true 1	always true 2
1. I find it difficult to climb stairs.	- 2	- 1	0	1	2
2. I suffer from breathing problems when I eat.	- 2	- 1	0	1	2
3. I can go out in the evening.	- 2	- 1	0	1	2
4. I often feel miserable.	- 2	- 1	0	1	2
5. I suffer from breathing problems even without physical exertion.	- 2	- 1	0	1	2
6. I often have a headache.	- 2	- 1	0	1	2
7. I have many friends and acquaintances.	- 2	- 1	0	1	2
8. I worry that my illness might worsen.	- 2	- 1	0	1	2
9. I go to sleep easily.	- 2	- 1	0	1	2
10. I can deal with other people easily.	- 2	- 1	0	1	2
11. I sometimes feel dizzy.	- 2	- 1	0	1	2
12. I wake up at night with breathing difficulties.	- 2	- 1	0	1	2
13. I am afraid of having breathing difficulties at night.	- 2	- 1	0	1	2
14. I often have neck pain.	- 2	- 1	0	1	2
15. I am largely confined to the house.	- 2	- 1	0	1	2
16. Housework is difficult for me.	- 2	- 1	0	1	2

SRI

How did you feel ***last week?*** For EVERY statement please mark the answer that best applies to you.

	completely untrue - 2	mostly untrue - 1	sometimes true 0	mostly true 1	always true 2
17. I often wake up at night.	- 2	- 1	0	1	2
18. I sleep through the night easily.	- 2	- 1	0	1	2
19. I am often short of breath.	- 2	- 1	0	1	2
20. I am optimistic about the future.	- 2	- 1	0	1	2
21. I feel lonely.	- 2	- 1	0	1	2
22. I have trouble breathing when I speak.	- 2	- 1	0	1	2
23. Visitors exhaust me.	- 2	- 1	0	1	2
24. I cough a lot.	- 2	- 1	0	1	2
25. There is often mucus in my airways.	- 2	- 1	0	1	2
26. I avoid situations where my breathing problems might embarrass me.	- 2	- 1	0	1	2
27. I feel good when I am with friends/ acquaintances.	- 2	- 1	0	1	2
28. I am afraid of having a bout of difficult breathing.	- 2	- 1	0	1	2
29. I have difficulties breathing during physical exertion.	- 2	- 1	0	1	2
30. I am irritated by the limitations caused by my illness.	- 2	- 1	0	1	2
31. My marriage/relationship is suffering because of my illness.	- 2	- 1	0	1	2
32. I can go shopping.	- 2	- 1	0	1	2
33. I can pursue all hobbies that interest me.	- 2	- 1	0	1	2

SRI

How did you feel ***last week?*** For EVERY statement please mark the answer that best applies to you.

	completely untrue - 2	mostly untrue - 1	sometimes true 0	mostly true 1	always true 2
34. I am often irritable.	- 2	- 1	0	1	2
35. My contact with friends/acquaintances is limited by my illness.	- 2	- 1	0	1	2
36. I am enjoying life.	- 2	- 1	0	1	2
37. I can take part in social events.	- 2	- 1	0	1	2
38. I am often sad.	- 2	- 1	0	1	2
39. My breathing difficulties bother me in public situations.	- 2	- 1	0	1	2
40. I am often nervous.	- 2	- 1	0	1	2
41. I can dress myself.	- 2	- 1	0	1	2
42. I am tired during the day.	- 2	- 1	0	1	2
43. I feel isolated.	- 2	- 1	0	1	2
44. I can cope well with my illness.	- 2	- 1	0	1	2
45. My breathing difficulties impair me in everyday activities.	- 2	- 1	0	1	2
46. My family life is suffering because of my illness.	- 2	- 1	0	1	2
47. I have broken off contact to other people because of my breathing problems.	- 2	- 1	0	1	2
48. My free-time opportunities are limited.	- 2	- 1	0	1	2
49. I am satisfied with life in general.	- 2	- 1	0	1	2

Thank you!

Appendix C: ESS

HOT HMV trial Questionnaires _ / _ / _

Epworth Sleepiness Score

This test is designed to see how sleepy you are. Answer using the following scale choosing the most appropriate number to how you usually feel in each of the following situations

0 = would never fall asleep
1 = slight chance of falling asleep
2 = moderate chance of falling asleep
3 = high chance of falling asleep

Sitting & reading	
Watching TV	
Sitting inactive in a public place	
Being a passenger in a motor vehicle for an hour or more	
Lying down in the afternoon	
Having a conversation	
Sitting quietly after lunch (without alcohol)	
Stopped for a few minutes in traffic while driving	
Total score	

v1 13/5/10

Appendix D: CRQ-SAI

McMASTER UNIVERSITY
CANADA

CHRONIC RESPIRATORY QUESTIONNAIRE

SELF-ADMINISTERED INDIVIDUALIZED FORMAT
(CRQ-SAI)

FIRST ADMINISTRATION

CHRONIC RESPIRATORY QUESTIONNAIRE
SELF-ADMINISTERED INDIVIDUALIZED FORMAT (CRQ-SAI)
FIRST ADMINISTRATION

Date completed: ☐☐ ☐☐ ☐☐☐☐
DAY MONTH YEAR

This questionnaire is designed to find out how you have been feeling during the last 2 weeks. In the first section, you will be asked to answer questions about activities which make some people feel short of breath. In the next section, you will answer questions about your mood and how you have been feeling.

Please read these instructions for completing this questionnaire:

- Please read each question carefully and then place an "x" in the box beside the answer that best describes you.
- If you are unsure about how to answer a question, please give the best answer you can.
- If you would like to change an answer, put a line through the box you want to change. Place an "x" in the box beside the option you would like to choose instead.
- There are no right or wrong answers.
- Your answers to this questionnaire will be kept confidential.

Please continue to the next page 1 - 8

CHRONIC RESPIRATORY QUESTIONNAIRE
SELF-ADMINISTERED INDIVIDUALIZED FORMAT (CRQ-SAI)
FIRST ADMINISTRATION

i. Please read the following list of activities which make some people with lung problems feel short of breath. Place an "x" in the box beside each activity **IF** you answer **YES** to **ALL** of the following four statements:

you have done the activity during the **LAST 2 WEEKS**
and it is something you do frequently
and it is important to your day to day life
and it makes you feel short of breath

ii. If you have not done the activity during the **LAST 2 WEEKS** or it does **NOT** make you feel short of breath then leave it blank.

iii. After you have read the list, please add any additional activities in the spaces provided. Only write down additional activities **IF** you answer **YES** to **ALL** of the following four statements:

you have done the activity during the **LAST 2 WEEKS**
and it is something you do frequently
and it is important to your day to day life
and it makes you feel short of breath

PLACE AN "X" IN THE BOX BESIDE ALL ACTIVITIES THAT APPLY

1 ☐ BEING ANGRY OR UPSET
2 ☐ HAVING A BATH OR SHOWER
3 ☐ BENDING
4 ☐ CARRYING, SUCH AS CARRYING GROCERIES
5 ☐ DRESSING
6 ☐ EATING
7 ☐ GOING FOR A WALK
8 ☐ DOING YOUR HOUSEWORK
9 ☐ HURRYING
10 ☐ MAKING A BED
11 ☐ MOPPING OR SCRUBBING THE FLOOR
12 ☐ MOVING FURNITURE
13 ☐ PLAYING WITH CHILDREN OR GRANDCHILDREN
14 ☐ PLAYING SPORTS
15 ☐ REACHING OVER YOUR HEAD
16 ☐ RUNNING, SUCH AS FOR A BUS
17 ☐ SHOPPING
18 ☐ WHILE TRYING TO SLEEP
19 ☐ TALKING
20 ☐ VACUUMING
21 ☐ WALKING AROUND YOUR OWN HOME
22 ☐ WALKING UPHILL
23 ☐ WALKING UPSTAIRS
24 ☐ WALKING WITH OTHERS ON LEVEL GROUND
25 ☐ PREPARING MEALS
26 ☐ _____ (Additional activity)
27 ☐ _____ (Additional activity)
28 ☐ _____ (Additional activity)
29 ☐ _____ (Additional activity)

Please continue to the next page

CHRONIC RESPIRATORY QUESTIONNAIRE
SELF-ADMINISTERED INDIVIDUALIZED FORMAT (CRQ-SAI)
FIRST ADMINISTRATION

We would now like you to look back at **page 2** and from the list of activities where you have placed an "x" in the box, tell us which is the most important activity in your day to day life.

To help you do this:

i. Look at the activities that you have placed an "x" in the box beside. Decide which activity is the most important to you in your day to day life. To do this, ask yourself, **"if I could choose one activity where I would no longer become short of breath doing which one would it be?"**

ii. Decide which is the first most important activity and write it on line 1 below. Decide which is the 2nd most important activity and write in on line 2. Continue doing this until you have rated a maximum of 5 activities.

iii. For each of the most important activities that you have recorded below, place an "x" in the box that best tells how much shortness of breath you have had while doing that activity during the **LAST 2 WEEKS**.

(Place an "x" in one box on each line)

Activities		Extremely short of breath	Very short of breath	Quite a bit short of breath	Moderate shortness of breath	Some shortness of breath	A little shortness of breath	Not at all short of breath
Activity	Name of activity							
1 ☐☐	_____	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
2 ☐☐	_____	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
3 ☐☐	_____	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
4 ☐☐	_____	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
5 ☐☐	_____	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐

Please continue to the next page

CHRONIC RESPIRATORY QUESTIONNAIRE
SELF-ADMINISTERED INDIVIDUALIZED FORMAT (CRQ-SAI)
FIRST ADMINISTRATION

These next questions ask you about your energy in general and how your mood has been during the **LAST 2 WEEKS**. Please put an "x" in a box, from 1 to 7, that best describes how you have felt.

6. In general, how much of the time during the **LAST 2 WEEKS** have you felt frustrated or impatient?

1	All of the time	☐	
2	Most of the time	☐	
3	A good bit of the time	☐	
4	Some of the time	☐	(Place an "X" in one box only)
5	A little of the time	☐	
6	Hardly any of the time	☐	
7	None of the time	☐	

7. How often during the **LAST 2 WEEKS** did you have a feeling of fear or panic when you had difficulty getting your breath?

1	All of the time	☐	
2	Most of the time	☐	
3	A good bit of the time	☐	
4	Some of the time	☐	(Place an "X" in one box only)
5	A little of the time	☐	
6	Hardly any of the time	☐	
7	None of the time	☐	

8. What about fatigue? How tired have you felt over the **LAST 2 WEEKS**?

1	Extremely tired	☐	
2	Very tired	☐	
3	Quite a bit of tiredness	☐	
4	Moderately tired	☐	(Place an "X" in one box only)
5	Somewhat tired	☐	
6	A little tired	☐	
7	Not at all tired	☐	

Please continue to the next page

CHRONIC RESPIRATORY QUESTIONNAIRE
SELF-ADMINISTERED INDIVIDUALIZED FORMAT (CRQ-SAI)
FIRST ADMINISTRATION

9. How often during the **LAST 2 WEEKS** have you felt embarrassed by your coughing or heavy breathing?

1	All of the time	☐	
2	Most of the time	☐	
3	A good bit of the time	☐	
4	Some of the time	☐	(Place an "X" in one box only)
5	A little of the time	☐	
6	Hardly any of the time	☐	
7	None of the time	☐	

10. The **LAST 2 WEEKS**, how much of the time did you feel very confident and sure that you could deal with your illness?

1	None of the time	☐	
2	A little of the time	☐	
3	Some of the time	☐	
4	A good bit of the time	☐	(Place an "X" in one box only)
5	Most of the time	☐	
6	Almost all of the time	☐	
7	All of the time	☐	

11. How much energy have you had in the **LAST 2 WEEKS**?

1	No energy at all	☐	
2	A little energy	☐	
3	Some energy	☐	
4	Moderately energetic	☐	(Place an "X" in one box only)
5	Quite a bit of energy	☐	
6	Very energetic	☐	
7	Full of energy	☐	

Please continue to the next page 5 - 8

CHRONIC RESPIRATORY QUESTIONNAIRE
SELF-ADMINISTERED INDIVIDUALIZED FORMAT (CRQ-SAI)
FIRST ADMINISTRATION

12. In general, how much of the time did you feel upset, worried or depressed during the **LAST 2 WEEKS**?

1	All of the time	☐	
2	Most of the time	☐	
3	A good bit of the time	☐	
4	Some of the time	☐	(Place an "X" in one box only)
5	A little of the time	☐	
6	Hardly any of the time	☐	
7	None of the time	☐	

13. How often during the **LAST 2 WEEKS**, did you feel you had complete control of your breathing problems?

1	None of the time	☐	
2	A little of the time	☐	
3	Some of the time	☐	
4	A good bit of the time	☐	(Place an "X" in one box only)
5	Most of the time	☐	
6	Almost all of the time	☐	
7	All of the time	☐	

14. How much of the time during the **LAST 2 WEEKS** did you feel relaxed and free of tension?

1	None of the time	☐	
2	A little of the time	☐	
3	Some of the time	☐	
4	A good bit of the time	☐	(Place an "X" in one box only)
5	Most of the time	☐	
6	Almost all of the time	☐	
7	All of the time	☐	

Please continue to the next page 6 - 8

CHRONIC RESPIRATORY QUESTIONNAIRE
SELF-ADMINISTERED INDIVIDUALIZED FORMAT (CRQ-SAI)
FIRST ADMINISTRATION

15. How often during the **LAST 2 WEEKS** have you felt low in energy?

1	All of the time	☐	
2	Most of the time	☐	
3	A good bit of the time	☐	
4	Some of the time	☐	(Place an "X" in one box only)
5	A little of the time	☐	
6	Hardly any of the time	☐	
7	None of the time	☐	

16. In general, how often during the **LAST 2 WEEKS** have you felt discouraged or down in the dumps?

1	All of the time	☐	
2	Most of the time	☐	
3	A good bit of the time	☐	
4	Some of the time	☐	(Place an "X" in one box only)
5	A little of the time	☐	
6	Hardly any of the time	☐	
7	None of the time	☐	

17. How often during the **LAST 2 WEEKS** have you felt worn out or sluggish?

1	All of the time	☐	
2	Most of the time	☐	
3	A good bit of the time	☐	
4	Some of the time	☐	(Place an "X" in one box only)
5	A little of the time	☐	
6	Hardly any of the time	☐	
7	None of the time	☐	

Please continue to the next page

CHRONIC RESPIRATORY QUESTIONNAIRE
SELF-ADMINISTERED INDIVIDUALIZED FORMAT (CRQ-SAI)
FIRST ADMINISTRATION

18. How happy, satisfied, or pleased have you been with your personal life during the **LAST 2 WEEKS**?

1	Very dissatisfied, unhappy most of the time	☐	
2	Generally dissatisfied, unhappy	☐	
3	Somewhat dissatisfied, unhappy	☐	
4	Generally satisfied, pleased	☐	(Place an "X" in one
5	Happy most of the time	☐	box only)
6	Very happy most of the time	☐	
7	Extremely happy, could not be more satisfied or pleased	☐	

19. How often during the **LAST 2 WEEKS** did you feel upset or scared when you had difficulty getting your breath?

1	All of the time	☐	
2	Most of the time	☐	
3	A good bit of the time	☐	
4	Some of the time	☐	(Place an "X" in one box only)
5	A little of the time	☐	
6	Hardly any of the time	☐	
7	None of the time	☐	

20. In general, how often during the **LAST 2 WEEKS** have you felt restless, tense or uptight?

1	All of the time	☐	
2	Most of the time	☐	
3	A good bit of the time	☐	
4	Some of the time	☐	(Place an "X" in one box only)
5	A little of the time	☐	
6	Hardly any of the time	☐	
7	None of the time	☐	

THANK YOU FOR COMPLETING THIS QUESTIONNAIRE 8 - 8

Appendix E: sleep hygiene diary

Study ID:

DAILY SLEEP LOG

During your Actigraphy study, we need a report of the times when you sleep, nap and how often you wake during sleep. IT IS IMPORTANT THAT YOU KEEP THIS RECORD FOR at least 10 DAYS. Each column begins a new day; the first column is an example for you to study.

Start Date	Example	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7
Naps: times and length you napped	2.00pm 45 mins 6.30pm 30 mins							
Time watch taken off & duration	Off at 10.30pm for 15mins							
Time in bed before lights out	30 mins							
Lights out	11pm							
Estimated time it took to fall asleep	45 mins							
Estimated no of awakenings in night/ duration	2am 20mins 4.30am 1hr							
Time of awakening next morning	7.30am							
Total nights sleep	7hrs							
Overall sleep quality for the night; Poor = 1 Average = 2 Good = 3	2							

EVENING ACTIVITIES:

DAY 1 **Start Date:** _____

DAY 2 _____

DAY 3 _____

DAY 4 _____

DAY 5 _____

DAY 6 _____

DAY 7 _____

Any Additional Comments:

HOT HMV trial sleep diary v1

Sleep Log Week 2

Start Date	Example	DAY 8	DAY 9	DAY 10	DAY 11	DAY 12	DAY 13	DAY 14
Naps: times and length you napped	2.00pm 45 mins 6.30pm 30 mins							
Time watch taken off & duration	Off at 10.30pm for 15mins							
Time in bed before lights out	30 mins							
Lights out	11pm							
Estimated time it took to fall asleep	45 mins							
Estimated no of awakenings in night/ duration	2am 20mins 4.30am 1hr							
Time of awakening next morning	7.30am							
Total nights sleep	7hrs							
Overall sleep quality for the night; Poor = 1 Average = 2 Good = 3	2							

EVENING ACTIVITIES:

DAY 8 _____

DAY 9 _____

DAY 10 _____

DAY 11 _____

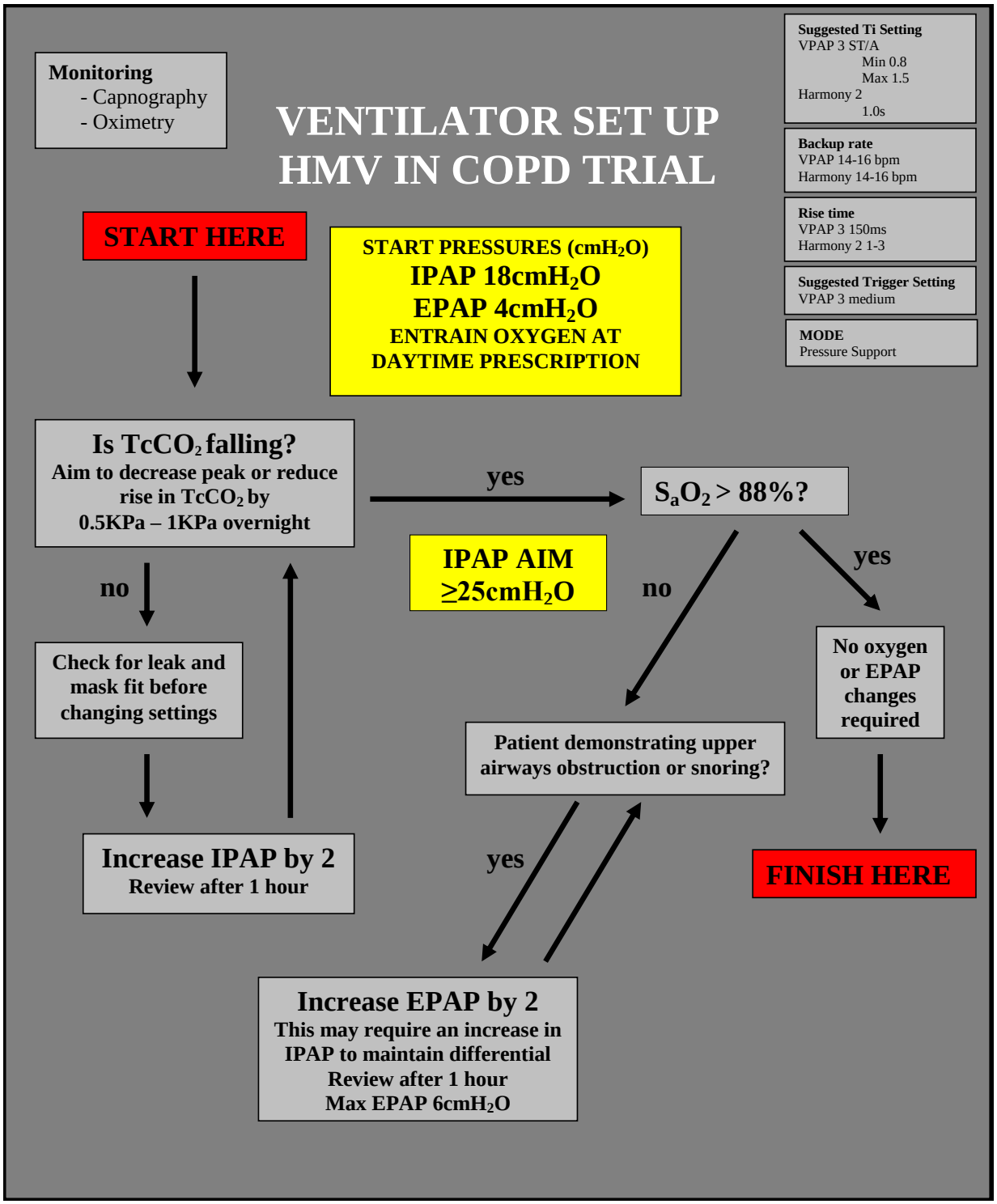
DAY 12 _____

DAY 13 _____

DAY 14 _____

Any Additional Comments:

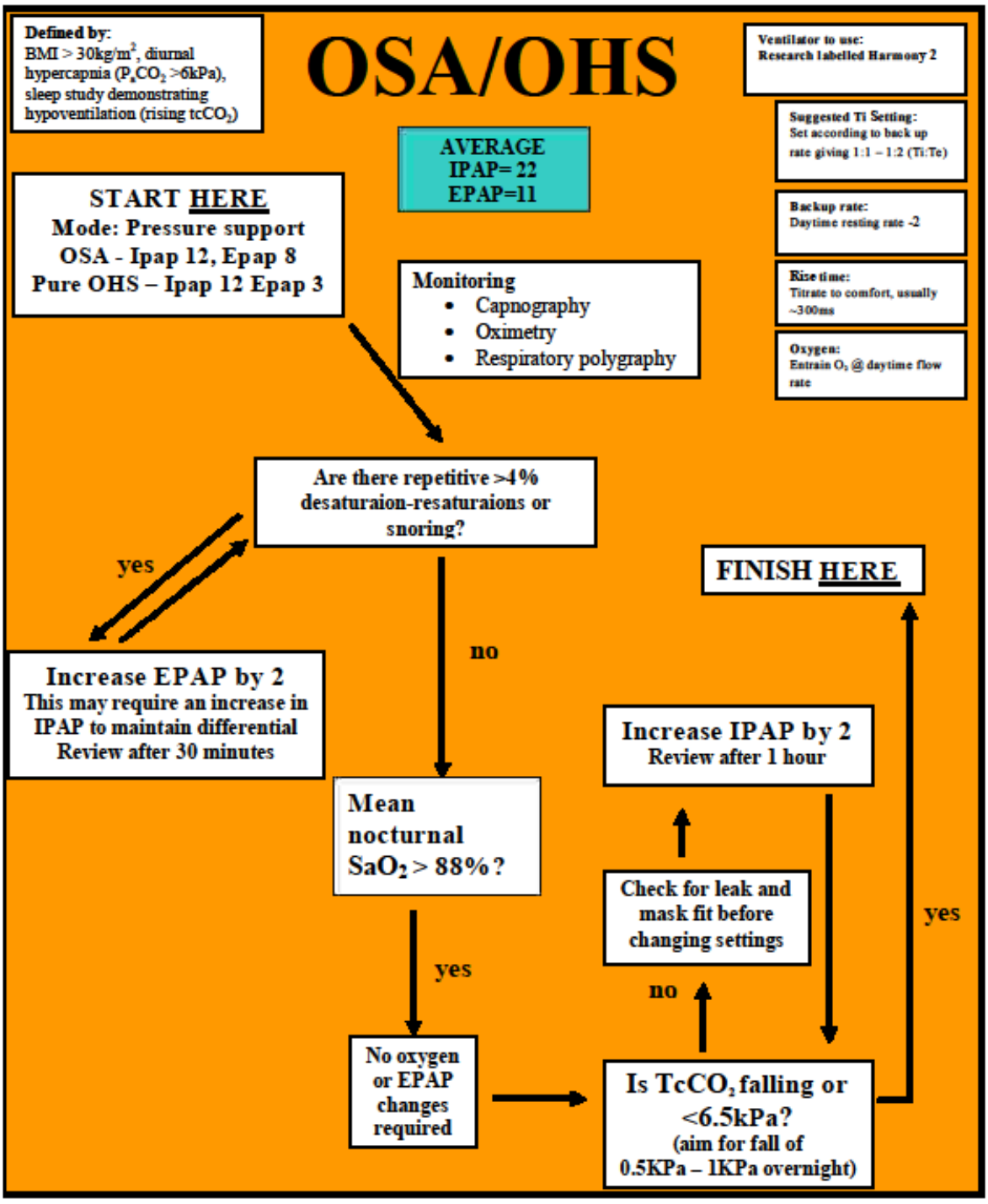
Appendix F: HOT-HMV titration protocol



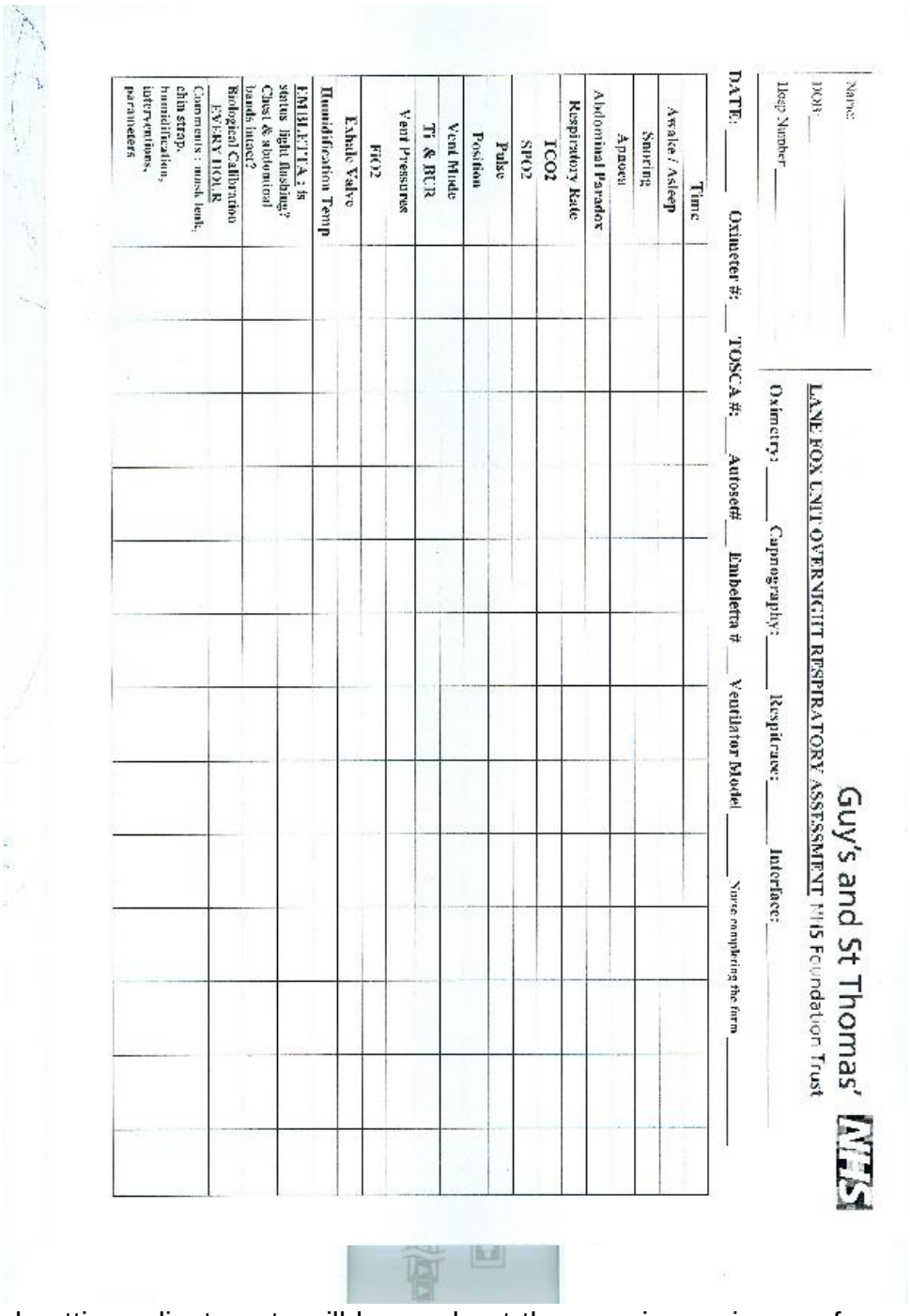
Appendix G: AVAPS overnight titration protocol

Patients randomised to the fixed bi-level arm underwent daytime NIV acclimatisation using the initiation settings provided on the protocol below. The daytime session was designed to provide the patient with time to familiarise themselves with the device and pressure settings but also to ensure adequate interface fitting. The interface should be fitted to provide patient comfort and with an unintentional leak of <30 L/min, with the aim to obtain a consistent leak of <15 L/min. Initial interface choice was a full face mask with nasal mask and chin strap used if full face mask was not tolerated. During acclimatisation patient synchronisation should be noted and back up rate altered to 2 less than resting rate. Rise time was modified to patient comfort. Patients had a nocturnal study with pressures titrated using the protocol provided below to adjust inspiratory and expiratory pressures in response to oximetry-capnometry readings and clinical observations.

AVAPS overnight setup Protocol (Fixed bi-level)



During overnight study hourly observations should be recorded in the nursing data sheet and attached to the downloaded respiratory sleep study report.



Guy's and St Thomas' NHS

LANE FOX UNIT OVERNIGHT RESPIRATORY ASSESSMENT NHS Foundation Trust

Name: _____

DOB: _____

Hosp Number: _____

Oximetry: _____ Capnography: _____ Respiraton: _____ Interface: _____

DATE: _____ Oximeter #: _____ TOSCA #: _____ Autoset# _____ Embeletta # _____ Ventilator Model _____ Nurse completing the form _____

Time												
Awake / Asleep												
Snoring												
Apnoea												
Abdominal Paradox												
Respiratory Rate												
TCO2												
SPO2												
Pulse												
Position												
Vent Mode												
Ti & BUR												
Vent Pressures												
FIO2												
Exhale Valve												
Humidification Temp												
EMBLETTA: is status light flashing? Chest & abdominal bands intact?												
Biological Calibration EVERY HOUR												
Comments : mask leak, chin strap, humidification, interventions, parameters												

Final setting adjustments will be made at the morning review performed by the supervising consultant along with decision on acceptability of overnight control of sleep disordered breathing and suitability for discharge.